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(54) Title: IDENTIFICATION OF POLYNUCLEOTIDES FOR PREDICTING ACTIVITY OF COMPOUNDS THAT INTERACT WITH AND/OR MODULATE PROTEIN TYROSINE KINASES AND/OR PROTEIN TYROSINE KINASE PATHWAYS IN BREAST CELLS



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(57) Abstract: The present invention describes polynucleotides that have been discovered to correlate to the relative intrinsic sensitivity or resistance of cells, e.g., breast cell lines, to treatment with compounds that interact with and modulate, e.g., inhibit, protein tyrosine kinases, such as, for example, members of the Src family of tyrosine kinases, e.g., Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as other protein tyrosine kinases, including, Bcr-abl, Jak, PDGFR, c-kit and Eph receptors. These polynucleotides have been shown, through a weighted voting cross validation program, to have utility in predicting the resistance and sensitivity of breast cell lines to the compounds. The expression level or phosphorylation status of some polynucleotides is regulated by treatment with a particular protein tyrosine kinase inhibitor compound, thus indicating that these polynucleotides are involved in the protein tyrosine kinase signal transduction

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pathway, e.g., Src tyrosine kinase. Such polynucleotides, whose expression levels correlate highly with drug sensitivity or resistance and which are modulated by treatment with the compounds, comprise polynucleotide predictor or marker sets useful in methods of predicting drug response, and as prognostic or diagnostic indicators in disease management, particularly in those disease areas, e.g., breast cancer, in which signaling through the protein tyrosine kinase pathway, such as the Src tyrosine kinase pathway, is involved with the disease process.



IDENTIFICATION OF POLYNUCLEOTIDES FOR PREDICTING ACTIVITY OF  
COMPOUNDS THAT INTERACT WITH AND/OR MODULATE PROTEIN  
TYROSINE KINASES AND/OR PROTEIN TYROSINE KINASE PATHWAYS IN  
BREAST CELLS

5

This application claims benefit to provisional application U.S. Serial No. 60/406,385 filed August 27, 2002, under 35 U.S.C. 119(e). The entire teachings of the referenced applications are incorporated herein by reference.

10

FIELD OF THE INVENTION

The present invention relates generally to the field of pharmacogenomics, and more specifically to new and alternative methods and procedures to determine drug sensitivity in patients, and particularly in patients with breast cancer. This invention allows the development of individualized genetic profiles which aid in treating  
15 diseases and disorders based on patient response at a molecular level.

BACKGROUND OF THE INVENTION

Breast cancer is a disease with extensive histoclinical heterogeneity. Although conventional histological and clinical features have been correlated with prognosis,  
20 the same apparent prognostic type of breast tumors vary widely in their responsiveness to therapy and consequent survival of the patient. New prognostic and predictive markers are needed to accurately foretell a patient's response to drugs in the clinic. Such markers would facilitate the individualization of therapy for each patient.

The problem may be solved by the identification of new parameters that can  
25 better predict a patient's sensitivity to treatment or therapy. The classification of patient samples is a crucial aspect of cancer diagnosis and treatment. The association of a patient's response to drug treatment with molecular and genetic markers can open up new opportunities for drug development in non-responding patients, or distinguish a drug's indication among other treatment choices because of higher confidence in the  
30 efficacy. Further, the pre-selection of patients who are likely to respond well to a medicine, drug, or combination therapy may reduce the number of patients needed in

a clinical study or accelerate the time needed to complete a clinical development program (M. Cockett et al., 2000, *Current Opinion in Biotechnology*, 11:602-609).

The major goal of pharmacogenomics research is to identify genetic markers that accurately predict a given patient's response to drugs in the clinic; such individualized genetic assessment would greatly facilitate personalized treatment. An approach of this nature is particularly needed in cancer treatment and therapy, where commonly used agents are ineffective in many patients, and side effects are frequent. The ability to predict drug sensitivity in patients is particularly challenging because drug responses reflect both the properties intrinsic to the target cells and also a host's metabolic properties. Efforts by those in the art to use genetic information to predict drug sensitivity have primarily focused on individual polynucleotides that have broad effects, such as the multidrug resistant polynucleotides, *mdr1* and *mrr1* (P. Sonneveld, 2000, *J. Intern. Med.*, 247:521-534).

The development of microarray technologies for large scale characterization of polynucleotide expression pattern makes it possible to systematically search for multiple molecular markers and to categorize cancers into distinct subgroups that are not evident by traditional histopathological methods (J. Khan et al., 1998, *Cancer Res.*, 58:5009-5013; A.A. Alizadeh et al., 2000, *Nature*, 403:503-511; M. Bittner et al., 2000, *Nature*, 406:536-540; J. Khan et al., 2001, *Nature Medicine*, 7(6):673-679; and T.R. Golub et al., 1999, *Science*, 286:531-537; U. Alon et al., 1999, *Proc. Natl. Acad. Sci. USA*, 96:6745-6750). Such technologies and molecular tools have made it possible to monitor the expression levels of a large number of transcripts within a cell at any given time (see, e.g., Schena et al., 1995, *Science*, 270:467-470; Lockhart et al., 1996, *Nature Biotechnology*, 14:1675-1680; Blanchard et al., 1996, *Nature Biotechnology*, 14:1649; and U.S. Pat. No. 5,569,588, issued Oct. 29, 1996 to Ashby et al.).

How differential polynucleotide expression is associated with health and disease is a basis of functional genomics, which is defined as the study of all of the polynucleotides expressed by a specific cell or a group of cells and the changes in their expression pattern during development, disease, or environmental exposure. Hybridization arrays, used to study polynucleotide expression, allow polynucleotide expression analysis on a genomic scale by permitting the examination of changes in

expression of literally thousands of polynucleotides at one time. In general, for hybridization arrays, gene-specific sequences (probes) are immobilized on a solid state matrix. These sequences are then queried with labeled copies of nucleic acids from biological samples (targets). The underlying theory is that the greater the  
5 expression of a gene, the greater the amount of labeled target and thus, the greater output of signal. (W.M. Freeman et al., 2000, *BioTechniques*, 29:1042-1055).

Recent studies have demonstrated that polynucleotide expression information generated by microarray analysis of human tumors can predict clinical outcome (L.J. van't Veer et al., 2002, *Nature*, 415:530-536; M. West et al., 2001, *Proc. Natl. Acad. Sci. USA*, 98:11462-11467; T. Sorlie et al., 2001, *Proc. Natl. Acad. Sci. USA*, 98:10869-10874; M. Shipp et al., 2002, *Nature Medicine*, 8(1):68-74). These findings  
10 bring hope that cancer treatment will be vastly improved by better predicting the response of individual tumors to therapy.

Needed in the art are new and alternative methods and procedures to  
15 determine drug sensitivity in patients and which are necessary to treat diseases and disorders, particularly cancers such as breast cancer, based on patient response at a molecular level. By using cultured cells as a model of *in vivo* effects, the present invention advantageously focuses on cell-intrinsic properties that are exposed in cell culture and involves identified polynucleotides that correlate with drug sensitivity.  
20 The presently described discovery and identification of polynucleotides/marker polynucleotides (predictor polynucleotides and polynucleotide sets) in cell lines assayed *in vitro* can be used to correlate with drug responses *in vivo*, and thus can be extended to clinical situations in which the same polynucleotides are used to predict responses to drugs and/or chemotherapeutic agents by patients, with particular regard  
25 to breast cancer patients.

### SUMMARY OF THE INVENTION

The present invention describes the identification of marker polynucleotides whose expression levels are highly correlated with drug sensitivity in breast cell lines  
30 that are either sensitive or resistant to protein tyrosine kinase inhibitor compounds. More particularly, the protein tyrosine kinases that are inhibited in accordance with the present invention include members of the Src family of tyrosine kinases, for

example, Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as other protein tyrosine kinases, including, Bcr-abl, Jak, PDGFR, c-kit and Eph receptors. For a review of these and other protein tyrosine kinases, see, for example, P. Blume-Jensen and T. Hunter, 2001, "Oncopolynucleotide Kinase Signaling", *Nature*, 411:355-365. Some  
5 of these polynucleotides are also modulated by the tyrosine kinase inhibitor compounds, in particular, src tyrosine kinase inhibitor compounds, which indicates their involvement in the protein tyrosine kinase signaling pathway. These polynucleotides or "markers" show utility in predicting a host's response to a drug and/or drug treatment. Similar expression pattern of these polynucleotides to breast  
10 cell lines is also seen in primary breast tumors which indicates co-regulation of these marker polynucleotides.

It is an aspect of this invention to provide a cell culture model to identify polynucleotides whose expression levels correlate with drug sensitivity of cells associated with a disease state, or with a host having a disease. In accordance with the  
15 present invention, oligonucleotide microarrays were utilized to measure the expression levels of a large number of polynucleotides in a panel of untreated cell lines, particularly breast cell lines, for which drug sensitivity to a protein tyrosine kinase inhibitor compound was determined. The determination of the polynucleotide expression profiles in the untreated cells allowed a prediction of chemosensitivity and  
20 the identification of marker polynucleotides whose expression levels highly correlated with sensitivity to drugs or compounds that modulate, preferably inhibit, protein tyrosine kinase or the pathway in which the protein tyrosine kinase, e.g., src tyrosine kinase, is involved. The marker polynucleotides are thus able to be utilized as one or more predictors to foresee a patient's response to drugs or drug treatments that  
25 directly or indirectly affect protein tyrosine kinase activity.

It is another aspect of the present invention to provide a method of determining or predicting if an individual requiring drug or chemotherapeutic treatment or therapy for a disease state, or a cancer or tumor of a particular type, e.g., a breast cancer or breast tumor, will successfully respond or will not respond to the  
30 drug or chemotherapeutic treatment or therapy prior to the administration of such treatment or chemotherapy. Preferably, the treatment or therapy involves a protein tyrosine kinase modulating agent, e.g., an inhibitor of the protein tyrosine kinase

activity. The protein tyrosine kinases whose activities can be inhibited by inhibitor compounds according to this invention include, for example, members of the Src family of tyrosine kinases, for example, Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as other protein tyrosine kinases, including, Bcr-abl, Jak, PDGFR, c-kit and Eph receptors. Also in accordance with the present invention, cells from a patient tissue sample, e.g., a breast tumor or cancer biopsy, are assayed to determine their polynucleotide expression pattern prior to treatment with a protein tyrosine kinase modulating compound or drug, preferably a src tyrosine kinase inhibitor. The resulting polynucleotide expression profile of the test cells before exposure to the compound or drug is compared with the polynucleotide expression pattern of the predictor set of polynucleotides that have been described and shown herein (Table 2). In addition, in such a method, the polynucleotide expression pattern of subsets of predictor polynucleotides, i.e., the sets of 15 and 7 polynucleotides as set forth in Tables 4-5, respectively, can also be used. These polynucleotides are derived from the control panel of the untreated cells that have been determined to be either resistant or sensitive to the drug or compound, i.e., FIG. 1 and Table 1.

Success or failure of treatment with a drug can be determined based on the polynucleotide expression pattern of cells from the test tissue (test cells), e.g., a tumor or cancer biopsy, as being relatively similar to or different from the polynucleotide expression pattern of the predictor set of polynucleotides. Thus, if the test cells show a polynucleotide expression profile which corresponds to that of the predictor set of polynucleotides in the control panel of cells which are sensitive to the drug or compound, it is highly likely or predicted that the individual's cancer or tumor will respond favorably to treatment with the drug or compound. By contrast, if the test cells show a polynucleotide expression pattern corresponding to that of the predictor set of polynucleotides of the control panel of cells which are resistant to the drug or compound, it is highly likely or predicted that the individual's cancer or tumor will not respond to treatment with the drug or compound.

It is a further aspect of this invention to provide screening assays for determining if a cancer patient will be susceptible or resistant to treatment with a drug or compound, particularly, a drug or compound directly or indirectly involved in a protein tyrosine kinase activity or a protein tyrosine kinase pathway. Such protein

tyrosine kinases include, without limitation, members of the Src family of tyrosine kinases, for example, Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as other protein tyrosine kinases, including, Bcr-abl, Jak, PDGFR, c-kit and Eph receptors.

5 In a more particular aspect, the present invention provides screening assays for determining if a cancer patient will be susceptible or resistant to treatment with a drug or compound, particularly, a drug or compound directly or indirectly involved in src tyrosine kinase activity or the src tyrosine kinase pathway.

It is another aspect of the present invention to provide a method of monitoring the treatment of a patient having a disease treatable by a compound or agent that  
10 modulates a protein tyrosine kinase, including members of the Src family of tyrosine kinases, for example, Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as other protein tyrosine kinases, including, Bcr-abl, Jak, PDGFR, c-kit and Eph receptors. This can be accomplished by comparing the resistance or sensitivity polynucleotide expression profile of cells from a patient tissue sample, e.g., a tumor or cancer biopsy,  
15 e.g., a breast cancer or tumor sample, prior to treatment with a drug or compound that inhibits the protein tyrosine kinase activity and again following treatment with the drug or compound. The isolated test cells from the patient's tissue sample are assayed to determine their polynucleotide expression pattern before and after exposure to a compound or drug, such as, e.g., a src tyrosine kinase inhibitor. The resulting  
20 polynucleotide expression profile of the test cells before and after treatment is compared with the polynucleotide expression pattern of the predictor set and subsets of polynucleotides that have been described and shown herein to be highly expressed in the control panel of cells that are either resistant or sensitive to the drug or compound. Thus, if a patient's response becomes one that is sensitive to treatment by  
25 a protein tyrosine kinase inhibitor compound, based on a correlation of the expression profile of the predictor polynucleotides, the patient's treatment prognosis can be qualified as favorable and treatment can continue. Also, if after treatment with a drug or compound, the test cells do not show a change in their polynucleotide expression profile that corresponds to the control panel of cells that are sensitive to the drug or  
30 compound, this can serve as an indicator that the current treatment should be modified, changed, or even discontinued. Such a monitoring process can indicate

success or failure of a patient's treatment with a drug or compound, and the monitoring processes can be repeated as necessary or desired.

It is a further aspect of the present invention to provide predictor polynucleotides and predictor sets of polynucleotides having both diagnostic and prognostic value in disease areas in which signaling through a protein tyrosine kinase or a protein tyrosine kinase pathway is of importance, e.g., in cancers and tumors, in immunological disorders, conditions or dysfunctions, or in disease states in which cell signaling and/or proliferation controls are abnormal or aberrant. Such protein tyrosine kinases whose direct or indirect modulation can be associated with a disease state or condition, include members of the Src family of tyrosine kinases, for example, Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as other protein tyrosine kinases, including, Bcr-abl, Jak, PDGFR, c-kit and Eph receptors. In accordance with this invention, the use of predictor polynucleotides, or a predictor polynucleotide set or subset (such as the predictor polynucleotides of Table 2, and the predictor polynucleotide subsets of Tables 4-5) is to forecast or foretell an outcome prior to having any knowledge about a biological system, or a cellular response.

It is yet another aspect of the present invention to assemble polynucleotides, such as those listed in Table 2, or the subset of polynucleotides as listed in Tables 4-5, that highly correlate with resistance or sensitivity to protein tyrosine kinase inhibitor drugs or compounds, into predictor polynucleotide sets, so as to predict, or reasonably foretell the effect of either the protein tyrosine inhibitor compounds, or compounds that affect the protein tyrosine kinase signaling pathway(s) in different biological systems, or for cellular responses. The predictor polynucleotide sets can be used in *in vitro* assays of drug response by test cells to predict *in vivo* outcome. In accordance with this invention, the various predictor polynucleotide sets described herein, or the combination of these predictor sets with other polynucleotides or other co-variants of these polynucleotides, can be used, for example, to predict how patients with cancer or a tumor might respond to therapeutic intervention with compounds that modulate protein tyrosine kinases, or modulate signaling through an entire protein tyrosine kinase regulatory pathway. The predictor sets of polynucleotides, or co-variants of these polynucleotides, can be used to predict how patients with a cancer or tumor respond to therapy employing compounds that modulate a tyrosine kinase, or the

activity of a tyrosine kinase, such as protein tyrosine kinase members of the Src family, for example, Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as other protein tyrosine kinases, including, Bcr-abl, Jak, PDGFR, c-kit and Eph receptors.

Another object of the present invention is to provide one or more specialized  
5 microarrays, e.g., oligonucleotide microarrays or cDNA microarrays, comprising those polynucleotides or combinations thereof, as described herein, showing expression profiles that correlate with either sensitivity or resistance to protein tyrosine kinase inhibitor compounds. Such microarrays can be employed in *in vitro* assays for assessing the expression level of the polynucleotides on the microarrays in  
10 the test cells from tumor biopsies, for example, and determining whether these test cells will be likely to be resistant or sensitive to the protein tyrosine kinase inhibitor compound(s). For example, a specialized microarray can be prepared using some or all of the polynucleotides, polynucleotide subsets, or combinations thereof, as described herein and shown in Tables 2, 4 and 5. Cells from a tissue or organ biopsy  
15 can be isolated and exposed to one or more inhibitor compounds. Following application of nucleic acids isolated from both untreated and treated cells to one or more of the specialized microarrays, the pattern of polynucleotide expression of the tested cells can be determined and compared with that of the predictor polynucleotide pattern from the control panel of cells used to create the predictor polynucleotide set  
20 on the microarray. Based upon the polynucleotide expression pattern results from the cells undergoing testing, it can be determined if the cells show a resistant or a sensitive profile of polynucleotide expression. Whether or not the tested cells from a tissue or organ biopsy will respond to a protein tyrosine kinase inhibitor compound, and the course of treatment or therapy, can then be determined or evaluated based on  
25 the information gleaned from the results of the specialized microarray analysis.

It is a further aspect of the present invention to provide a kit for determining or predicting drug susceptibility or resistance by a patient having a disease, with particular regard to a cancer or tumor, namely, a breast cancer or tumor. Such kits are useful in a clinical setting for testing a patient's biopsied tumor or cancer sample, for  
30 example, to determine or predict if the patient's tumor or cancer will be resistant or sensitive to a given treatment or therapy with a drug, compound, chemotherapy agent, or biological agent that is directly or indirectly involved with modification, preferably,



- inhibition, of the activity of a protein tyrosine kinase or a cell signaling pathway involving protein tyrosine kinase activity. Provided in the kit are one or more microarrays, e.g., oligonucleotide microarrays or cDNA microarrays, comprising those polynucleotides that correlate with resistance and sensitivity to protein tyrosine
- 5 kinase modulators, particularly, inhibitors of members of the Src family of protein tyrosine kinases, for example, Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as inhibitors of the Bcr-abl, Jak, PDGFR, c-kit and Eph receptors protein tyrosine kinases; and, in suitable containers, the modulator agents/compounds for use in testing cells from patient tissue specimens or patient samples; and instructions for use.
- 10 In addition, kits contemplated by the present invention can include reagents or materials for the monitoring of the expression of the predictor or marker polynucleotides of the invention at the level of mRNA or protein, using other techniques and systems practiced in the art, e.g., RT-PCR assays, which employ primers designed on the basis of one or more of the predictor polynucleotides
- 15 described herein, immunoassays, such as enzyme linked immunosorbent assays (ELISAs), immunoblotting, e.g., Western blots, or *in situ* hybridization, and the like, as further described herein. The kits according to the present invention can also comprise predictor polynucleotides as set forth in Table 2, and/or one or more of the predictor polynucleotide subsets as presented in Tables 4-5 herein.
- 20 Another aspect of the present invention is to provide one or more polynucleotides among those of the predictor polynucleotides identified herein that can serve as targets for the development of drug therapies for disease treatment. Such targets can be particularly applicable to treatment of breast disease, such as breast cancers or tumors. Because these predictor polynucleotides are differentially
- 25 expressed in sensitive and resistant cells, their expression pattern is correlated with the relative intrinsic sensitivity of cells to treatment with compounds that interact with and/or inhibit protein tyrosine kinases, including members of the Src family of protein tyrosine kinases, for example, Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as the Bcr-abl, Jak, PDGFR, c-kit and Eph receptors protein tyrosine kinases.
- 30 Accordingly, the polynucleotides highly expressed in resistant cells can serve as targets for the development of new drug therapies for those tumors which are resistant to protein tyrosine kinase inhibitor compounds.

Yet another object of the present invention is to provide antibodies, either polyclonal or monoclonal, directed against one or more of the protein tyrosine kinase biomarker polypeptides, or peptides thereof, encoded by the predictor polynucleotides. Such antibodies can be used in a variety of ways, for example, to  
5 purify, detect, and target the protein tyrosine kinase biomarker polypeptides of the present invention, including both *in vitro* and *in vivo* diagnostic, detection, screening, and/or therapeutic methods, and the like. Included among the protein tyrosine kinase biomarker polypeptides of this invention are members of the Src family of protein tyrosine kinases, for example, Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as  
10 the Bcr-abl, Jak, PDGFR, c-kit and Eph receptors protein tyrosine kinases.

Yet another object of the present invention is to provide antisense reagents, including siRNA, RNAi, and ribozyme reagents, directed against one or more of the protein tyrosine kinase biomarker polypeptides, or peptides thereof, encoded by the predictor polynucleotides. Such antisense reagents can be used in a variety of ways,  
15 for example, to detect, to target, and inhibit the expression of the protein tyrosine kinase biomarker polypeptides of the present invention, including both *in vitro* and *in vivo* diagnostic, detection, screening, and/or therapeutic methods, and the like. Included among the protein tyrosine kinase biomarker polypeptides of this invention are members of the Src family of protein tyrosine kinases, for example, Src, Fgr, Fyn,  
20 Yes, Blk, Hck, Lck and Lyn, as well as the Bcr-abl, Jak, PDGFR, c-kit and Eph receptors protein tyrosine kinases.

The invention also relates to an antisense compound 8 to 30 nucleotides in length that specifically hybridizes to a nucleic acid molecule encoding the human protein tyrosine kinase biomarker polypeptides of the present invention, wherein said  
25 antisense compound inhibits the expression of the human protein tyrosine kinase biomarker polypeptides.

The invention further relates to a method of inhibiting the expression of the human protein tyrosine kinase biomarker polypeptides of the present invention in human cells or tissues comprising contacting said cells or tissues *in vitro*, or *in vivo*,  
30 with an antisense compound of the present invention so that expression of the protein tyrosine kinase biomarker polypeptides is inhibited.

The present invention is also directed to a method of identifying a compound that modulates the biological activity of protein tyrosine kinase biomarker polypeptides, comprising the steps of, (a) combining a candidate modulator compound with protein tyrosine kinase biomarker polypeptides in the presence of an  
5 antisense molecule that antagonizes the activity of the protein tyrosine kinase biomarker polypeptides selected from the group consisting of SEQ ID NO:534 thru 557, and (b) identifying candidate compounds that reverse the antagonizing effect of the peptide.

The present invention is also directed to a method of identifying a compound  
10 that modulates the biological activity of protein tyrosine kinase biomarker polypeptides, comprising the steps of, (a) combining a candidate modulator compound with protein tyrosine kinase biomarker polypeptides in the presence of a small molecule that antagonizes the activity of the protein tyrosine kinase biomarker polypeptides selected from the group consisting of SEQ ID NO:534 thru 557, and (b)  
15 identifying candidate compounds that reverse the antagonizing effect of the peptide.

The present invention is also directed to a method of identifying a compound that modulates the biological activity of protein tyrosine kinase biomarker polypeptides, comprising the steps of, (a) combining a candidate modulator compound with protein tyrosine kinase biomarker polypeptides in the presence of a  
20 small molecule that agonizes the activity of the protein tyrosine kinase biomarker polypeptides selected from the group consisting of SEQ ID NO:534 thru 557, and (b) identifying candidate compounds that reverse the agonizing effect of the peptide.

Further aspects, features, and advantages of the present invention will be better appreciated upon a reading of the detailed description of the invention when  
25 considered in connection with the accompanying figures or drawings.

## DESCRIPTION OF THE FIGURES

The file of this patent contains at least one Figure executed in color. Copies of this patent with color Figure(s) will be provided by the Patent and Trademark Office  
30 upon request and payment of the necessary fee.

FIG. 1 illustrates a polynucleotide expression pattern according to the present invention. The 137 polynucleotides that highly correlated with a resistance/sensitivity

phenotype classification of the 23 breast cell lines for the protein tyrosine kinase inhibitor compound BMS-A are shown. Each row corresponds to a polynucleotide, with the columns corresponding to expression level in the different cell lines. Expression levels for each polynucleotide were normalized across all 23 breast cell lines such that the median is 0 and the standard derivation is 1. The expression levels greater than the median are shaded in red, and those below the mean are shaded in green. The individual polynucleotides encoding the protein tyrosine kinase biomarkers of the invention are indicated at the right (details of the biomarkers are also shown in the Table 2). The cell lines labeled in red are classified as resistant, and those labeled in blue are classified as sensitive to BMS-A according to their IC<sub>50</sub>.

FIG. 2 The examples of polynucleotides whose expression levels are not only correlated with the sensitivity or resistance of breast cell lines to treatment with a protein tyrosine kinase inhibitor compound (e.g., BMS-A), but also differentially down regulated by treatment with the compound. Eleven breast cell lines (5 sensitive and 6 resistant cell lines as indicated in bold in the Table 1) were used in a drug treatment study. Cells were treated with or without the BMS-A compound (0.4  $\mu$ M) in 0.1% DMSO for 24 hours. Expression profiling was performed, the polynucleotide expression of a cell line treated with drug was compared pair-wisely to the polynucleotide expression of the same cell line without drug treatment. Five sensitive cell lines without drug treatment are indicated with lightly shaded bars ("A" side of graph); five sensitive cell lines with drug treatment are indicated in darkly shaded bars ("A" side of graph); six resistant cell lines without drug treatment are indicated in darkly shaded bars ("B" side of graph); six resistant cell lines with drug treatment are indicated in lightly shaded bars ("B" side of graph).

FIG. 3 The examples of polynucleotide whose expression is down regulated by BMS-A compound treatment in a dose and time dependent manner in a prostate cell line PC3. Cells are treated without or with 0.025  $\mu$ M, 0.1  $\mu$ M and 0.4  $\mu$ M of the BMS-A compound for 4 hours or 24 hours. The relative polynucleotide expression level of treated cells is compared to the corresponding untreated control which is set to 1. Drug concentrations and time of treatment are indicated.

FIG. 4 Immunoblot analysis of EphA2 protein level and tyrosine phosphorylation status in nine breast tumor cell lines. Cells were treated with 0.1  $\mu$ M

BMS-A for 1 hour. Cell lysates were immuno-precipitated with EphA2 antibody and blotted with EphA2 antibody (to assess EphA2 protein level) or anti-phosphotyrosine antibody (to assess EphA2 tyrosine phosphorylation status). Cell lines with or without drug treatment are indicated. The results indicate that EphA2 protein level does not  
5 change upon one hour drug treatment, but the phosphorylation of tyrosine residues is dramatically decreased with the drug treatment.

FIG. 5 shows the error rates of different predictor sets comprising the marker polynucleotides with differential selection and combination for the BMS-A protein tyrosine kinase inhibitor compound in the leave-one-out cross validation tests. The  
10 Genecluster software was used to select polynucleotides and predict classifications using a "weighted-voting leave-one-out cross-validation algorithm", as described herein. A different number of polynucleotides was selected in the predictor set from (i) the 137 polynucleotides, or (ii) the 40 polynucleotides modulated by BMS-A treatment as shown in Table 2, for predicting resistant and sensitive classes to BMS-A  
15 in the breast cell lines. FIG. 5 demonstrates that a different selection and different combination of polynucleotides in a predictor set achieve different error rates in the leave-one-out cross validation. When the predictor sets were selected from 137 polynucleotides as shown in Table 2, the lowest error rate of 6.3% was achieved in the leave-one-out cross validation with 15 markers. Another predictor set comprised of 7  
20 polynucleotides selected from the 40 polynucleotides that were modulated by the drug treatment achieved an error rate of 3.1%. These results indicate that polynucleotides which are not only correlated with drug sensitivity, but also modulated by the drug, can provide a better and more accurate prediction in a predictor set.

FIG. 6 shows the error rate comparison for predicting the sensitivity  
25 classification of compound BMS-A in the breast cell lines and random permutation tests in leave-one-out cross validation. When a predictor set contained either 7 or 15 polynucleotides selected from different polynucleotide groups, the error rate of the leave-one-out cross validation tests for predicting sensitivity of BMS-A in the 23 breast cell lines was 3.1% and 6.3% respectively. In contrast, the real error rates  
30 ranged from 30% to 83% when the same number of polynucleotides in a predictor set was used in 20 cases in which classification for the breast cell lines was randomly assigned. This result demonstrates that the error rate value for predicting sensitivity

of BMS-A in the 23 breast cell lines is significantly lower than the error rate for predicting sensitivity for the 23 breast cell lines when their classification is randomly assigned in 20 cases.

FIG. 7 The expression pattern of the 137 marker polynucleotides in 134 primary breast tumors. These 137 polynucleotides are highly correlated with a resistance/sensitivity phenotype classification of the 23 breast cell lines for the protein tyrosine kinase inhibitor compound BMS-A according to the present invention (as shown in FIG.1). Each row corresponds to a gene, with the columns corresponding to expression level in the different breast tumor samples. Expression levels for each polynucleotide were normalized across all 134 breast tumor samples such that the median is 0 and the standard derivation is 1. The expression levels greater than the median are shaded in red, and those below the mean are shaded in green. The order of individual polynucleotides encoding the protein tyrosine kinase biomarkers of the invention are the same as indicated in FIG.1. The expression pattern clearly shows that a group of primary breast tumors (as indicated by the arrow) highly expressed sensitive markers of protein tyrosine kinase inhibitor compound of the invention. By contrast, another different group highly expressed resistant markers.

#### DESCRIPTION OF THE TABLES

Table 1 presents the resistance/sensitivity phenotype classification of the 23 breast cell lines for the protein tyrosine kinase inhibitor compound BMS-A based on  $IC_{50}$  results. The  $IC_{50}$  for each cell line was assessed in by MTS assays as described in Example 1 (Methods). The mean  $IC_{50}$  values along with standard deviations (SD) were calculated from 2 to 5 individual determinations for each cell line as shown. The  $IC_{50}$  unit is  $\mu M$ . The mean  $IC_{50}$  for each cell line was log-transformed to  $\log_{10}(IC_{50})$  and the mean  $\log_{10}(IC_{50})$  across the 23 breast cell lines for BMS-A was calculated and used to normalize the  $IC_{50}$  data for each cell line. The cell lines with a  $\log_{10}(IC_{50})$  below the mean  $\log_{10}(IC_{50})$  were defined as sensitive to the compound, while those having a  $\log_{10}(IC_{50})$  above the mean  $\log_{10}(IC_{50})$  were considered to be resistant. The cell lines presented in bold were used in the drug induction study as described herein.

TABLE 1

#	Cell Lines	mean IC <sub>50</sub> (μM) to BMS-A	SD	Log(IC <sub>50</sub> )	Normalized Log(IC <sub>50</sub> )	Classification
1	MDA-MB-157	0.0055	0.0035	-2.25924	-2.25405	Sensitive
2	MDA-MB-231	0.0095	0.0058	-2.02422	-2.03843	Sensitive
3	HCC1954	0.0242	0.0172	-1.61621	-1.66411	Sensitive
4	HCC70	0.0337	0.0160	-1.47214	-1.53193	Sensitive
5	BT-20	0.1652	0.1036	-0.78195	-0.89871	Sensitive
6	HCC1806	0.2194	0.1508	-0.65884	-0.78576	Sensitive
7	HS578T	0.6472	0.5885	-0.18898	-0.35469	Sensitive
8	HCC1419	2.5093	0.2280	0.399548	0.18525	Resistant
9	SK-BR-3	2.7534	0.8410	0.439867	0.22224	Resistant
10	AU-565	5.2399	3.2627	0.719322	0.47863	Resistant
11	HCC38	6.6327	3.1673	0.821688	0.57254	Resistant
12	BT-474	6.7375	4.1515	0.828502	0.57880	Resistant
13	MDA-MB-468	7.1258	4.0960	0.852833	0.60112	Resistant
14	HCC1428	7.2926	4.1436	0.862881	0.61034	Resistant
15	MDA-MB-435S	7.7800	2.3643	0.89098	0.63612	Resistant
16	H3396	8.1950	3.2549	0.91355	0.65682	Resistant
17	BT-549	9.0576	1.1419	0.957014	0.69670	Resistant
18	ZR-75-30	9.2632	0.5827	0.966762	0.70564	Resistant
19	MCF7	>9.5238	1.95E-07	0.978811	0.71670	Resistant
20	MCF7/Her2	>9.5238	1.8E-07	0.978811	0.71670	Resistant
21	MDA-MB-436	>9.5238	1.51E-07	0.978811	0.71670	Resistant
22	ZR-75-1	>9.5238	1.8E-07	0.978811	0.71670	Resistant
23	MDA-MB-453	>9.5238		0.978811	0.71670	Resistant
	Mean IC <sub>50</sub> across all 23 cell lines	5.2744		0.197626		
	SD	3.9565		1.08998		

Table 2 shows a polynucleotide list derived from three analysis algorithms that demonstrated a high correlation between expression pattern and resistance/sensitivity classification to BMS-A. The polynucleotide number, relative expression pattern, i.e., sensitive or resistant, Genbank Accession number, polynucleotide description, Unigene cluster number, SEQ ID NO: for the nucleic acid sequence of the gene, SEQ ID NO: for the amino acid sequence coded for by the polynucleotide (if available) and PID (protein ID), are presented in Table 2. For each gene, the DNA and encoded amino acid sequence represented by SEQ ID NOs. in Table 2 are set forth in the Sequence Listing.

TABLE 2

Markers highly correlated to BMS-A in expression pattern and resistance/sensitivity classification

Gene No.	Highly Expressed in	Genbank Accession #	Modulated by BMS-A	Unigene Title	Unigene Cluster	DNA SEQ ID NO:	Amino Acid SEQ ID NO:	Protein ID
1	Sensitive cells	NM_004431	yes	EphA2	Hs.171596	1	138	NP_004422
2	Sensitive cells	AF025304		EphB2	Hs.125124	2	139	AA094602
3	Sensitive cells	AU147399	yes	caveolin 1, caveolae protein, 22kD	Hs.74034	3	140	NP_001744
4	Sensitive cells	NM_001233	yes	caveolin 2	Hs.139851	4	141	NP_001224
5	Sensitive cells	NM_000700	yes	annexin A1	Hs.78225	5	142	NP_000691
6	Sensitive cells	NM_004039		annexin A2	Hs.406239	6	143	NP_004030
7	Sensitive cells	BG107577		parvin, alpha	Hs.44077	7	144	Q9NVD7
8	Sensitive cells	BE965369	yes	coagulation factor II (thrombin) receptor-like 1	Hs.154299	8	145	XP_003671
9	Sensitive cells	NM_001993	yes	coagulation factor III (thromboplastin, tissue factor)	Hs.62192	9	146	NP_001984
10	Sensitive cells	BF792126		Homo sapiens, clone IMAGE:4344858, mRNA	Hs.432974	10	147	P1_453619
11	Sensitive cells	BE856341		layilin	Hs.133015	11	148	Q96NF3
12	Sensitive cells	U17496		proteasome (prosome, macropain) subunit, beta type, 8 (large multifunctional protease 7)	Hs.180062	12	149	P28062
13	Sensitive cells	NM_002800		proteasome (prosome, macropain) subunit, beta type, 9 (large multifunctional protease 2)	Hs.381081	13	150	NP_002791
14	Sensitive cells	NM_000311		prion protein (p27-30) (Creutzfeld-Jakob disease, Gerstmann-Strausler-Scheinker syndrome, fatal familial insomnia)	Hs.74621	14	151	P04156
15	Sensitive cells	NM_003739	yes	aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type II)	Hs.78183	15	152	NP_003730
16	Sensitive cells	NM_020639		ankyrin repeat domain 3	Hs.55565	16	153	NP_065690
17	Sensitive cells	AF208043	yes	interferon, gamma-inducible protein 16	Hs.155530	17	154	Q16666
18	Sensitive cells	AF003837	yes	jagged 1 (Alagille syndrome)	Hs.91143	18	155	P78504
19	Sensitive cells	BC002832	yes	butyrophilin, subfamily 3, member A2	Hs.87497	19	156	AAF76140
20	Sensitive cells	NM_006994	yes	butyrophilin, subfamily 3, member A3	Hs.167741	20	157	NP_008925
21	Sensitive cells	AF327443		calpastatin	Hs.359682	21	158	XP_051211



Gene No.	Highly Expressed in	Genbank Accession #	Modulated by BMS-A	Unigene Title	Unigene Cluster	DNA SEQ ID NO:	Amino Acid SEQ ID NO:	Protein ID
22	Sensitive cells	NM_021615	yes	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 6	Hs.157439	22	159	NP_067628
23	Sensitive cells	AF104857	yes	CDC42 effector protein (Rho GTPase binding) 3	Hs.260024	23	160	NP_006440
24	Sensitive cells	AL136896		suppressor of cytokine signaling 5	Hs.169836	24	161	O75159
25	Sensitive cells	AL565621	yes	coactosin-like protein	Hs.289092	25	162	AAH16702
26	Sensitive cells	BF111719		alkylglycerone phosphate synthase	Hs.22580	26	163	O00116
27	Sensitive cells	N36770		dual specificity phosphatase 10	Hs.177534	27	164	NP_009138
28	Sensitive cells	AW575374	yes	ELK3, ETS-domain protein (SRF accessory protein 2)	Hs.288555	28	165	NP_005221
29	Sensitive cells	AW269335	yes	endothelial differentiation, lysophosphatidic acid G-protein-coupled receptor, 2	Hs.75794	29	166	NP_001392
30	Sensitive cells	BC001247	yes	epithelial protein lost in neoplasm beta	Hs.10706	30	167	Q9UHB6
31	Sensitive cells	BE669858		hypothetical protein FLJ39885	Hs.319825	31	168	NP_689916
32	Sensitive cells	NM_000127		exostoses (multiple) 1	Hs.184161	32	169	NP_000118
33	Sensitive cells	NM_002589		BH-protocadherin (brain-heart)	Hs.34073	33	170	O60245
34	Sensitive cells	AI133452		fibrinogen, gamma polypeptide	Hs.75431	34	171	AAH21674
35	Sensitive cells	NM_006101		highly expressed in cancer, rich in leucine heptad repeats	Hs.58169	35	172	NP_006092
36	Sensitive cells	AL135264		ESTs, Moderately similar to hypothetical protein FLJ20489	Hs.406100	36		
37	Sensitive cells	NM_014164		FXVD domain-containing ion transport regulator 5	Hs.333418	37	173	NP_054883
38	Sensitive cells	BC003502		small fragment nuclease	Hs.7527	38	174	Q9Y3B8
39	Sensitive cells	AA780067		heparan sulfate (glucosamine) 3-O-sulfotransferase 3B1	Hs.159572	39	175	Q9Y662
40	Sensitive cells	AA702248	yes	Homo sapiens cDNA FL14241 fis, clone OVARC1000533	Hs.183765	40		
41	Sensitive cells	BC004372		CD44 antigen (homing function and Indian blood group system)	Hs.169610	41	176	Q9UI36
42	Sensitive cells	BF688144		Homo sapiens mRNA; cDNA DKFZp762O2215 (from clone DKFZp762O2215)	Hs.331666	42		
43	Sensitive cells	NM_018067		hypothetical protein FLJ10350	Hs.177596	43	177	NP_060537
44	Sensitive cells	BG111761		guanine nucleotide binding protein (G protein), gamma 12	Hs.8107	44	178	Q9UBI6
45	Sensitive cells	NM_017821		nucleoredoxin	Hs.374534	45	179	NP_060291

Gene No.	Highly Expressed in	Genbank Accession #	Modulated by BMS-A	Unigene Title	Unigene Cluster	DNA SEQ ID NO:	Amino Acid SEQ ID NO:	Protein ID
46	Sensitive cells	AA722799		endothelial and smooth muscle cell-derived neuropilin-like protein	Hs.173374	46	180	Q96PD2
47	Sensitive cells	BC006436		hypothetical protein MGC13105	Hs.22744	47	181	AAH06436
48	Sensitive cells	NM_006548	yes	IGF-II mRNA-binding protein 2	Hs.30299	48	182	NP_006539
49	Sensitive cells	NM_002194		inositol polyphosphate-1-phosphatase	Hs.32309	49	183	NP_002185
50	Sensitive cells	BG251556		KIAA1949 protein	Hs.101150	50	184	BAB85535
51	Sensitive cells	J03202		laminin, gamma 1 (formerly LAMB2)	Hs.432855	51	185	NP_002284
52	Sensitive cells	NM_000245	yes	met proto-oncogene (hepatocyte growth factor receptor)	Hs.316752	52	186	NP_000236
53	Sensitive cells	NM_002444		moesin	Hs.170328	53	187	NP_002435
54	Sensitive cells	NM_012334	yes	myosin X	Hs.61638	54	188	NP_036466
55	Sensitive cells	AI769569		ESTs	Hs.112472	55		
56	Sensitive cells	NM_002633	yes	phosphoglucosyltransferase 1	Hs.1869	56	189	NP_002624
57	Sensitive cells	BC004295	yes	polymyrase I and transcript release factor	Hs.29759	57	190	O00535
58	Sensitive cells	NM_016205		platelet derived growth factor C	Hs.43080	58	191	Q9UL22
59	Sensitive cells	NM_004815	yes	PTPL1-associated RhoGAP 1	Hs.70983	59	192	NP_004806
60	Sensitive cells	NM_002872		ras-related C3 botulinum toxin substrate 2 (rho family, small GTP binding protein Rac2)	Hs.301175	60	193	NP_002863
61	Sensitive cells	AF329267		SH3-domain kinase binding protein 1	Hs.153260	61	194	XP_039010
62	Sensitive cells	AI572079		snail homolog 2 (Drosophila)	Hs.93005	62	195	AAH14890
63	Sensitive cells	NM_001549		interferon-induced protein with tetratricopeptide repeats 4	Hs.181874	63	196	O14879
64	Sensitive cells	D50683		transforming growth factor, beta receptor II (70-80kD)	Hs.82028	64	197	NP_003233
65	Sensitive cells	NM_005902		MAD (mothers against decapentaplegic, Drosophila) homolog 3	Hs.288261	65	198	Q92940
66	Sensitive cells	NM_014452		tumor necrosis factor receptor superfamily, member 21	Hs.159651	66	199	NP_055267
67	Sensitive cells	AB017644		ubiquitin-conjugating enzyme E2E 3 (homologous to yeast UBC4/5)	Hs.4890	67	200	XP_096160
68	Sensitive cells	BC002323		zyxin	Hs.75873	68	201	Q15942
69	Resistant cells	AL157452		Homo sapiens mRNA; cDNA DKFZp761C1712 (from clone DKFZp761C1712)	Hs.4774	69		

Gene No.	Highly Expressed in	Genbank Accession #	Modulated by BMS-A	Unigene Title	Unigene Cluster	DNA SEQ ID NO:	Amino Acid SEQ ID NO:	Protein ID
70	Resistant cells	BF752277		hypothetical protein FLJ20151	Hs.279916	70	202	Q9NXM9
71	Resistant cells	BF512299		ESTs	Hs.438672	71		
72	Resistant cells	AL049381	yes	Homo sapiens mRNA; cDNA DKFZp586j2118 (from clone DKFZp586j2118)	Hs.21851	72		
73	Resistant cells	NM_002585	yes	pre-B-cell leukemia transcription factor 1	Hs.155691	73	203	NP_002576
74	Resistant cells	T68445		anaphase-promoting complex subunit 7	Hs.52763	74	204	Q96AC4
75	Resistant cells	BF308645		PRex1 KIAA1415 protein	Hs.109315	75	205	Q8TCU6
76	Resistant cells	AF088867	yes	anterior gradient 2 (Xenopus laevis) homolog	Hs.413945	76	206	AF088867_1
77	Resistant cells	NM_004040	yes	Human HepG2 3' region cDNA, clone hmd1f06.	Hs.204354	77	207	NP_004031
78	Resistant cells	AF151810	yes	serologically defined colon cancer antigen 28	Hs.84700	78	208	Q9Y365
79	Resistant cells	NM_004252		transmembrane 7 superfamily member 2	Hs.31130	79	209	NP_004243
80	Resistant cells	NM_005749	yes	transducer of ERBB2, 1	Hs.178137	80	210	NP_005740
81	Resistant cells	NM_003225	yes	trefoil factor 1 (breast cancer, estrogen-inducible sequence expressed in)	Hs.350470	81	211	NP_003216
82	Resistant cells	AA181060	yes	Homo sapiens cDNA FLJ31753 fis, clone NT2R12007468	Hs.349283	82		
83	Resistant cells	AL050025		adaptor-related protein complex 1, gamma 1 subunit	Hs.5344	83	212	CAB43244
84	Resistant cells	NM_001089		ATP-binding cassette, sub-family A (ABC1), member 3	Hs.26630	84	213	NP_001080
85	Resistant cells	NM_004915		ATP-binding cassette, sub-family G (WHITE), member 1	Hs.10237	85	214	NP_004906
86	Resistant cells	AL523275		CALM1 calmodulin 1 (phosphorylase kinase, delta)	Hs.374441	86	215	AAH00454
87	Resistant cells	NM_001218	yes	carbonic anhydrase XII	Hs.5338	87	216	NP_001209
88	Resistant cells	NM_016286		dicarbonyl/L-xylulose reductase	Hs.9857	88	217	NP_057370
89	Resistant cells	BC000185		carnitine palmitoyltransferase I, liver	Hs.259785	89	218	AAH00185
90	Resistant cells	NM_005505		scavenger receptor class B, member 1	Hs.180616	90	219	NP_005496
91	Resistant cells	NM_016048		CGI-111 protein	Hs.11085	91	220	NP_057132
92	Resistant cells	BC000195		CGI-81 protein	Hs.279583	92	221	NP_057109
93	Resistant cells	NM_001306		claudin 3	Hs.25640	93	222	NP_001297
94	Resistant cells	BC000021		cytochrome b-561	Hs.355264	94	223	NP_001906
95	Resistant cells	W68084		EGF-like-domain, multiple 5	Hs.5599	95	224	Q9H1U4
96	Resistant cells	AA825563	yes	ESTs	Hs.445708	96		

Gene No.	Highly Expressed in	Genbank Accession #	Modulated by BMS-A	Unigene Title	Unigene Cluster	DNA SEQ ID NO:	Amino Acid SEQ ID NO:	Protein ID
97	Resistant cells	BE887449		Homo sapiens cDNA FLJ34170 fis, clone FCBBF3015396.	Hs.32112	97		
98	Resistant cells	AI123815	yes	hypothetical protein FLJ21963	Hs.13222	98	225	Q9H6R3
99	Resistant cells	AI308862		RAB21, member RAS oncogene family	Hs.184627	99	226	Q9UL25
100	Resistant cells	AW006352		EST	Hs.159643	100		
101	Resistant cells	AL554277		chromosome 17 open reading frame 28	Hs.11067	101	227	Q9NT34
102	Resistant cells	BG289001		hypothetical protein LOC253782	Hs.387400	102		
103	Resistant cells	AI935915		hypothetical protein LOC112868	Hs.97837	103	228	XP_053402
104	Resistant cells	NM_017689	yes	hypothetical protein FLJ20151	Hs.279916	104	229	NP_060159
105	Resistant cells	NM_017966		hypothetical protein FLJ20847	Hs.13479	105	230	NP_060436
106	Resistant cells	AI923458		Williams Beuren syndrome chromosome region 21	Hs.182476	106	231	NP_112585
107	Resistant cells	NM_000597		insulin-like growth factor binding protein 2 (36kD)	Hs.433326	107	232	NP_000588
108	Resistant cells	U90304		iroquois homeobox protein 5	Hs.25351	108	233	P78411
109	Resistant cells	NM_004968		islet cell autoantigen 1 (69kD)	Hs.167927	109	234	NP_004959
110	Resistant cells	AL563283		androgen-induced basic leucine zipper	Hs.372924	110	235	NP_570968
111	Resistant cells	AA135522		KIAA0089 protein	Hs.82432	111	236	AAH28726
112	Resistant cells	AI867102	yes	solute carrier family 9 (sodium/hydrogen exchanger), isoform 3 regulatory factor 1	Hs.184276	112	237	XP_051621
113	Resistant cells	AW134976		KIAA0984 protein	Hs.11912	113	238	BAA76828
114	Resistant cells	AW665865		KIAA1069 protein	Hs.193143	114	239	BAA83021
115	Resistant cells	AB051487		nucleoporin 210	Hs.270404	115	240	BAB40814
116	Resistant cells	AB050049		methylcrotonoyl-Coenzyme A carboxylase 2 (beta)	Hs.167531	116	241	Q9HCC0
117	Resistant cells	NM_016835		microtubule-associated protein tau	Hs.101174	117	242	NP_058519
118	Resistant cells	AK002075		myelin gene expression factor 2	Hs.44268	118	243	NP_057216
119	Resistant cells	NM_000933		Homo sapiens mRNA; cDNA DKFZp434E235 (from clone DKFZp434E235)	Hs.348724	119	244	NP_000924
120	Resistant cells	AI435670		prostate epithelium-specific Ets transcription factor	Hs.79414	120	245	NP_036523
121	Resistant cells	NM_006443		putative c-Myc-responsive	Hs.109752	121	246	NP_006434
122	Resistant cells	AW263542		ESTs	Hs.403937	122		AAH15948

Gene No.	Highly Expressed in	Genbank Accession #	Modulated by BMS-A	Unigene Title	Unigene Cluster	DNA SEQ ID NO:	Amino Acid SEQ ID NO:	Protein ID
123	Resistant cells	AF153330		dual specificity phosphatase 16	Hs.20281	123	247	Q9BY84
124	Resistant cells	BC002702		solute carrier family 25 (mitochondrial carrier; ornithine transporter) member 15	Hs.78457	124	248	Q9Y619
125	Resistant cells	NM_006416		solute carrier family 35 (CMP-sialic acid transporter), member 1	Hs.82921	125	249	NP_006407
126	Resistant cells	NM_030674		solute carrier family 38, member 1	Hs.18272	126	250	NP_109599
127	Resistant cells	AF212371		spinster-like protein	Hs.379091	127	251	AAH08325
128	Resistant cells	AF096304		solute carrier family 19 (thiamine transporter), member 2	Hs.30246	128	252	AAD09765
129	Resistant cells	AK000948		trichorhinophalangeal syndrome I	Hs.26102	129	253	Q9UHF7
130	Resistant cells	AI859834		ESTs, Moderately similar to hypothetical protein FLJ20489	Hs.445020	130		
131	Resistant cells	BF512846		ESTs	Hs.442762	131		
132	Resistant cells	NM_022969	yes	fibroblast growth factor receptor 2 (bacteria-expressed kinase, keratinocyte growth factor receptor, craniofacial dysostosis 1, Crouzon syndrome, Pfeiffer syndrome, Jackson-Weiss syndrome)	Hs.278581	132	254	NP_075258
133	Resistant cells	AA741493	yes	ESTs	Hs.143842	133		
134	Resistant cells	NM_001424		epithelial membrane protein 2	Hs.29191	134	255	P54851
135	Resistant cells	AW242920	yes	ESTs	Hs.129368	135		
136	Resistant cells	W44413		small protein effector 1 of Cdc42	Hs.22065	136	256	Q9HB17
137	Resistant cells	AK021717		Homo sapiens cDNA FLJ11655 fis, clone HEMBA1004554	Hs.287436	137		

Table 3 presents a resistance/sensitivity prediction of the 23 breast cell lines for BMS-A in the 'leave one out' cross validation test using a Weighted Voting algorithm. The true class is assigned as in Table 1, based on the IC<sub>50</sub> results. The predicted class was determined by using the optimal 15 and 7 polynucleotides as the predictor set to predict the resistance or sensitive class. These polynucleotides were selected either from the 137 polynucleotides derived from three analysis methods as shown in Table 2, or from 40 drug treatment modulated polynucleotides as indicated in Table 2. "S" represents Sensitive; "R" represents Resistant. The PS score refers to prediction strength for each prediction made on a cell line by the predictor set. The PS score ranges from 0 to 1, i.e., corresponding from low to high confidence in making the prediction. The error predictions are indicated by an asterisk (\*).

TABLE 3

Cell Line	True Class	15 markers from 137 polynucleotides in Table 2			7 modulated markers from 40 polynucleotides as indicated in Table 2		
		Predicted Class	PS score	Error?	Predicted Class	PS score	Error?
MDAMB157	S	S	0.627		S	0.696	
MDAMB231	S	S	0.857		S	1.000	
HCC1954	S	S	0.416		S	0.847	
HCC70	S	S	0.695		S	1.000	
BT20	S	S	0.586		S	0.794	
HCC1806	S	S	0.985		S	1.000	
Hs578T	S	S	0.775		S	0.570	
HCC1419	R	R	1.000		R	1.000	
SkBr3	R	R	0.852		R	0.992	
AU565	R	R	0.629		R	0.763	
HCC38	R	S	0.101	*	S	0.501	*
BT474	R	R	0.938		R	1.000	
MDAMB468	R	R	0.392		R	0.416	
HCC1428	R	R	0.623		R	0.939	
MDAMB435S	R	S	0.723	*	R	0.324	
H3396	R	R	1.000		R	1.000	
BT549	R	R	0.029		R	0.012	
Zr-75-30	R	R	0.958		R	1.000	
MCF7	R	R	0.911		R	1.000	
Her2MCF7	R	R	0.991		R	1.000	
MDAMB436	R	R	0.340		R	0.412	
Zr-75-1	R	R	1.000		R	1.000	
MDAMB453	R	R	0.983		R	1.000	

Table 4 lists the predictor set of 15 polynucleotides used in prediction as shown in Table 3. These 15 polynucleotides were selected from the 137

polynucleotides derived from three analysis methods as shown in Table 2. The relative expression pattern, i.e., sensitive or resistant, polynucleotide description and Unigene cluster number for this 15 predictor polynucleotide subset are indicated in Table 4.

5

TABLE 4

Highly Expressed in:	Modulated by BMS-A	Unigene Title	Unigene Cluster No
Sensitive cells		EphB2	Hs.125124
Sensitive cells		parvin, alpha	Hs.44077
Sensitive cells	yes	coagulation factor II (thrombin) receptor-like 1	Hs.154299
Sensitive cells	yes	aldo-keto reductase family 1, member C3	Hs.78183
Sensitive cells	yes	interferon, gamma-inducible protein 16	Hs.155530
Sensitive cells	yes	jagged 1 (Alagille syndrome)	Hs.91143
Sensitive cells		hypothetical protein MGC13105	Hs.22744
Sensitive cells		snail homolog 2 (Drosophila)	Hs.93005
Resistant cells		Homo sapiens mRNA cDNA DKFZp761C1712	Hs.4774
Resistant cells	yes	Homo sapiens cDNA FLJ31753 fis, clone NT2RI2007468	Hs.349283
Resistant cells		ATP-binding cassette, sub-family A (ABC1), member 3	Hs.26630
Resistant cells		CGI-81 protein	Hs.279583
Resistant cells	yes	ESTs	Hs.445708
Resistant cells		EST	Hs.159643
Resistant cells		hypothetical protein LOC112868	Hs.97837

Table 5 lists the predictor set of 7 polynucleotides used in prediction as shown in Table 3. These 7 polynucleotides were selected from the 40 polynucleotides that were modulated by drug treatment as indicated in Table 2. The relative expression pattern, i.e., sensitive or resistant, polynucleotide description and Unigene cluster number for this 7 predictor polynucleotide subset are indicated in Table 5.

10

TABLE 5

Highly Expressed in:	Modulated by BMS-A	Unigene Title	Unigene Cluster No
Resistant cells	yes	Homo sapiens cDNA FLJ31753 fis, clone NT2RI2007468	Hs.349283
Sensitive cells	yes	jagged 1 (Alagille syndrome)	Hs.91143
Sensitive cells	yes	interferon, gamma-inducible protein 16	Hs.155530
Sensitive cells	yes	coagulation factor II (thrombin) receptor-like 1	Hs.154299
Resistant cells	yes	ESTs	Hs.445708
Sensitive cells	yes	aldo-keto reductase family 1, member C3	Hs.78183
Sensitive cells	yes	polymerase I and transcript release factor	Hs.29759

Table 6 lists the representative RT-PCR primer sets for each of the protein tyrosine kinase biomarker polynucleotides of the present invention. The SEQ ID NO: for each RT-PCR primer is provided (SEQ ID NO:257 thru 530).

5

TABLE 6

Genbank Accession No.	RT-PCR Primer Type	Rt-PCR Primer Sequence	SEQ ID NO:
NM_004431	Forward Primer	TCCTCACACTAAGAGGGCAGA	257
NM_004431	Reverse Primer	ACCTCAACACAACCAAGCATC	258
AF025304	Forward Primer	TCAGTGAGTACAACGCCACAG	259
AF025304	Reverse Primer	CTTCTCCTGGATGCTTGTCTG	260
NM_001753	Forward Primer	CCACCTTCACTGTGACGAAAT	261
NM_001753	Reverse Primer	CCAGATGTGCAGGAAAGAGAG	262
NM_001233	Forward Primer	AGCTGTCTGCACATCTGGATT	263
NM_001233	Reverse Primer	CCTGGGGTCCAAGTATTCAAT	264
NM_000700	Forward Primer	CATCAAGCCATGAAAGGTGTT	265
NM_000700	Reverse Primer	ACAAAGAGCCACCAGGATTTT	266
NM_004039	Forward Primer	GAAGTGTGTTCCCAAGTGGA	267
NM_004039	Reverse Primer	AACCAGGTTTCAGGAAAGCATT	268
BG107577	Forward Primer	TTTCGTGAACAAGCACCTGA	269
BG107577	Reverse Primer	ATGAGCTCAAAGGCAAAGGA	270
BE965369	Forward Primer	GTTTAAAATCCGGATTGGCAT	271
BE965369	Reverse Primer	GTGGCCGTGATAATTTTGTAA	272
NM_001993	Forward Primer	AAAATGGAAGGAAATTGGGTG	273
NM_001993	Reverse Primer	TGCCCAGAATACCAATGTCTC	274
BF792126	Forward Primer	TCGGTGAATTCAAGGACCAT	275
BF792126	Reverse Primer	GCTGCCTTCAAGGATCTCAC	276
E856341	Forward Primer	TGCCAGGTAAAGCTCTGTCC	277
E856341	Reverse Primer	GTCCTGTGGATGAGCATGTG	278
U17496	Forward Primer	ATCTCCAGAGCTCGCTTTACC	279
U17496	Reverse Primer	TTCACCCGTAAGGCACTAATG	280
NM_002800	Forward Primer	TATGGTTATGTGGATGCAGCA	281
NM_002800	Reverse Primer	AGATGACTCGATGGTCCACAC	282
NM_000311	Forward Primer	CCGAGTAAGCCAAAACCAA	283
NM_000311	Reverse Primer	CTCATCCATGGGCCTGTAGT	284
NM_003739	Forward Primer	GGTAGGGAACTTTCACCAACA	285
NM_003739	Reverse Primer	CTTGAGTCCTGGCTTGTTGAG	286
NM_020639	Forward Primer	TACTTGGGTGAGTCCTTGTGG	287
NM_020639	Reverse Primer	GACTCTTAGGCCTGTGGCTCT	288
AF208043	Forward Primer	GGAGTAAGGTGTCCGAGGAAC	289
AF208043	Reverse Primer	CTGACATTTGGCCACTGTTTT	290
AF003837	Forward Primer	CCTGTAACATAGCCCGAAACA	291
AF003837	Reverse Primer	AGTTGTCTCCATCCACACAGG	292
BC002832	Forward Primer	ACGTGTATGCAGATGGAAAGG	293
BC002832	Reverse Primer	CAGAGGCTGTGACGTTGTGTA	294
NM_006994	Forward Primer	AATTTGTGCAAGTTGGGAGATG	295
NM_006994	Reverse Primer	TGATCTCTACCCTGCAGCTGT	296
AF327443	Forward Primer	CATCTGACTTCACCTGTGGGT	297
AF327443	Reverse Primer	TTCTGACTGTCCCTGCTGACT	298
NM_021615	Forward Primer	ACCCCGACGTCTTCTACCTAA	299



Genbank Accession No.	RT-PCR Primer Type	Rt-PCR Primer Sequence	SEQ ID NO:
NM_021615	Reverse Primer	GCAGATAGGCATCAAACACGT	300
AF104857	Forward Primer	AGTTCCCTGGGCATAATGAGT	301
AF104857	Reverse Primer	AACATGAGAGCTTGGGATCCT	302
AL136896	Forward Primer	AGCCGAATCCACTCTCATGT	303
AL136896	Reverse Primer	TAACAAGGCACAGCAAGCAG	304
AL565621	Forward Primer	CTCAGACCTTTGCCCTTCTCT	305
AL565621	Reverse Primer	TCCGGCTCAGACTGAATAAGA	306
BF111719	Forward Primer	CACACATGGGCATTTGCTTA	307
BF111719	Reverse Primer	GGATATGCAGTGGGAAGGAA	308
BC020608	Forward Primer	CACCGAGAATCCTTACACCAA	309
BC020608	Reverse Primer	CAGAATCCATCCTCCTTCCTC	310
AW575374	Forward Primer	CATGCACACACACAGAATG	311
AW575374	Reverse Primer	TTTCCTTTGGAACTGGGATT	312
NM_001401	Forward Primer	CTTGCTGAATTCAACTCTGCC	313
NM_001401	Reverse Primer	AAACCACAGAGTGGTCATTGC	314
BC001247	Forward Primer	AGGAGAAGGAAGACAAGCCAG	315
BC001247	Reverse Primer	CTTGCTGATTTCGTCTTCAGG	316
BE669858	Forward Primer	CTGCTTGAGACTGTTCTGGCT	317
BE669858	Reverse Primer	GATTAGAGGGCTTCCTCATGG	318
NM_000127	Forward Primer	CAAGGGGAAGAGGTACCTGAC	319
NM_000127	Reverse Primer	TCTGTCACAGCGAGAATCCTT	320
NM_002589	Forward Primer	GACTCTGGGCGTCTCTGAAG	321
NM_002589	Reverse Primer	CAGCAACAAGCCAGTCTCAA	322
AI133452	Forward Primer	ACATCATGAGTTGGTCCTTGC	323
AI133452	Reverse Primer	AATCTGCAATGCCACAGGTAG	324
NM_006101	Forward Primer	TCCTCATACATGGCCTCACA	325
NM_006101	Reverse Primer	TGTCGGCACCACATCAAAA	326
AL135264	Forward Primer	GGTGCAGGTTGACACTGAAA	327
AL135264	Reverse Primer	AAGGTTACACAGGACACAGG	328
NM_014164	Forward Primer	ATCACAGGCATCATCATCCTC	329
NM_014164	Reverse Primer	GGTTGTCAGCTCCTGTTTCTG	330
BC003502	Forward Primer	GGGGTGTAGGTGGGAGTCAC	331
BC003502	Reverse Primer	AGTGCCTTCAGCCAAAATGT	332
AA780067	Forward Primer	GCCATCCTCTTGATAAGCTGA	333
AA780067	Reverse Primer	TCTTCCAGGATTCTCTTTGG	334
AA702248	Forward Primer	GATTGCAGATCCTATGCAGGA	335
AA702248	Reverse Primer	GCATCCAGGACAACACAAAGT	336
BC004372	Forward Primer	AAGGTGGAGCAAAACACAACC	337
BC004372	Reverse Primer	TCCACTTGGCTTTCTGTCTCT	338
BF688144	Forward Primer	CAAGTGCCCATTTAGGTTTGA	339
BF688144	Reverse Primer	ACTGACAGATGGCTCATTTGG	340
NM_018067	Forward Primer	GAACACCAGAGACACTCCTGC	341
NM_018067	Reverse Primer	ACATCCTGGTAGGTGATGCAG	342
BG111761	Forward Primer	CGCATCTGTCCAGCATCTTA	343
BG111761	Reverse Primer	CAAAACCGGGACGCTAACT	344
NM_017821	Forward Primer	AGAAACAGTGGATCACGTTGG	345
NM_017821	Reverse Primer	TTCCAAGGGAATACCCAAAAC	346
AA722799	Forward Primer	GTTTCCACTTTTCCCAGTGC	347
AA722799	Reverse Primer	TCACATGAAACGATTCTCTGCT	348
BC006436	Forward Primer	AATGTCAAAAGTGTGGGCAAG	349
BC006436	Reverse Primer	ATGTGGACCGAGTAAAGGCTT	350
NM_006548	Forward Primer	CAGTCCC GG TAGATATCCAT	351
NM_006548	Reverse Primer	TCTTCGGCTAGTTGGTCTCA	352

Genbank Accession No.	RT-PCR Primer Type	Rt-PCR Primer Sequence	SEQ ID NO:
NM_002194	Forward Primer	TGATTTGCCACAGTTGGTGTA	353
NM_002194	Reverse Primer	CTAGGTATGCGTCTCTGCAGG	354
BG251556	Forward Primer	CAGCCTGGTTTACAAATTCCA	355
BG251556	Reverse Primer	TGGGGAAAACCTAAGGCAAAGT	356
J03202	Forward Primer	CAACAATGAAGCCTGCTCTTC	357
J03202	Reverse Primer	CCTGCTTCAGTGAGAGAATGG	358
NM_000245	Forward Primer	AGGACCGGTTTCATCAACTTCT	359
NM_000245	Reverse Primer	TCAATGTAGGACTGGTCCGTC	360
NM_002444	Forward Primer	AAATGGTGCCTTCAAGACCTT	361
NM_002444	Reverse Primer	CCGGCCTATACTCCTACAAGG	362
NM_012334	Forward Primer	TAATGGTGGTCTGAACAAGGC	363
NM_012334	Reverse Primer	AGTTGGCCCAAGTCCTTAAAA	364
AI769569	Forward Primer	CATGGAGGAGCCATACAACA	365
AI769569	Reverse Primer	TTTGTCTGCTCCCAAATTC	366
NM_002633	Forward Primer	TGCTTTGTATGAGACCCCAAC	367
NM_002633	Reverse Primer	CATCTTTCTCACGGATGTGGT	368
BC004295	Forward Primer	AGAAGACAGAGAGGTCAGCCC	369
BC004295	Reverse Primer	TGGGACCCTAATTTTCTGGAC	370
NM_016205	Forward Primer	ACCCTTGAGTTTTCGCCTCT	371
NM_016205	Reverse Primer	GGATCAAAGCAAAACCTGGA	372
NM_004815	Forward Primer	GCCCCITTTGTATAGGACTGC	373
NM_004815	Reverse Primer	AATTCCAGTGAGGCACAAATG	374
NM_002872	Forward Primer	CAAGACCTGCCTTCTCATCAG	375
NM_002872	Reverse Primer	GAAGACGTCCGTCTGTGGATA	376
AF329267	Forward Primer	CAATTCTCTCAGCAGACCTGG	377
AF329267	Reverse Primer	ACCACGGAGTCAAAACCTTCT	378
AI572079	Forward Primer	CCCCAAGGCACATACTGTAA	379
AI572079	Reverse Primer	TGCCCATTTGTTGAACTAAAGC	380
NM_001549	Forward Primer	GAACATGCTGACCAAGCAGA	381
NM_001549	Reverse Primer	CAGTTGTGTCCACCCTTCCT	382
D50683	Forward Primer	AACAATACTGGCTGATCACCG	383
D50683	Reverse Primer	CATGGAGTGTGATCACTGTGG	384
NM_005902	Forward Primer	GGACTGCAGTGTGGAGTTCA	385
NM_005902	Reverse Primer	GAGAGGGGAGGGAGACAGAC	386
NM_014452	Forward Primer	GGTTTATAAGCCTTTGCCAGG	387
NM_014452	Reverse Primer	GTGGGAAAAGTCACACTGCAT	388
AB017644	Forward Primer	CTCCTCCTAATTGCAGTGTCTG	389
AB017644	Reverse Primer	GTGATAGATTCTGGTGC GGAA	390
BC002323	Forward Primer	CCTCAGGTCCAACCTCATGT	391
BC002323	Reverse Primer	GTGCCCCAATTTTGTATTG	392
AL157452	Forward Primer	AGCCTTGTCTCCCTTGGATT	393
AL157452	Reverse Primer	TCAGTTGCCCCTCTACAACC	394
BF752277	Forward Primer	AAGGCCCTGGATTCTCACTC	395
BF752277	Reverse Primer	GCCAGGACACCTTCAGAGAG	396
BF512299	Forward Primer	AAGAGCCTCCCAAAGGAAA	397
BF512299	Reverse Primer	GGGAAATGAAAGTGGCAAGA	398
AL049381	Forward Primer	TTGTTGGTTTTATTCTCCCCC	399
AL049381	Reverse Primer	CAGTTGGAATCAAAAGGGACA	400
NM_002585	Forward Primer	AGTGAGGAAGCCAAAGAGGAG	401
NM_002585	Reverse Primer	TTTGGCAGCATAAATATTGGC	402
T68445	Forward Primer	CAGAGAGGGAACCACCAGAG	403
T68445	Reverse Primer	CCCTGGGGAAATTAATGA	404
BF308645	Forward Primer	CTCTGTCCGGAAAGGAGAGA	405

Genbank Accession No.	RT-PCR Primer Type	Rt-PCR Primer Sequence	SEQ ID NO:
BF308645	Reverse Primer	GAACTTTGACGACACCGACA	406
AF088867	Forward Primer	CTCTGGCCAGAGATACCACAG	407
AF088867	Reverse Primer	CATCAAGGGTTTGTGCTTGT	408
NM_004040	Forward Primer	AACTATGTGGCCGACATTGAG	409
NM_004040	Reverse Primer	CACCGAGAAGCACATGAGAAT	410
AF151810	Forward Primer	CCTGAAGAACCGTGATGTCAT	411
AF151810	Reverse Primer	CTGTGCTCTGGATGAGGTAGC	412
NM_004252	Forward Primer	CACATCCCCTTTCTTGACAAA	413
NM_004252	Reverse Primer	GATGAGGCACTCAGTGAGGAG	414
NM_005749	Forward Primer	TTGAAACCTAATTTTGTGGCG	415
NM_005749	Reverse Primer	AAATGTTGACACGTCTCCTGG	416
NM_003225	Forward Primer	CCTAATACCATCGACGTCCCT	417
NM_003225	Reverse Primer	AGCTCTGGGACTAATCACCGT	418
AA181060	Forward Primer	AAAAGGCTGACAACTGACCA	419
AA181060	Reverse Primer	TCACAGCCTAGGTAAGAGCCA	420
AL050025	Forward Primer	CAGGTACGAATTTTGCGGTTA	421
AL050025	Reverse Primer	TCGCAATCCACTCTCTGACTT	422
NM_001089	Forward Primer	CTCCTTCAGCTTCATGGTCAG	423
NM_001089	Reverse Primer	TCTGGCTCAGAGTCATCCAGT	424
NM_004915	Forward Primer	CAACCCAGCAGATTTTGTTCAT	425
NM_004915	Reverse Primer	CGAGGTCTCTCTTGTGGTCTG	426
AL523275	Forward Primer	TCTTTGCATTGAGATTGGTCC	427
AL523275	Reverse Primer	ACCGTGAAAAATGCACATCTC	428
NM_001218	Forward Primer	CCTTCAATCCGTCCTATGACA	429
NM_001218	Reverse Primer	GGAAGCAGCTCTTCAATGTTG	430
NM_016286	Forward Primer	GAGTGAATGCAGTAAACCCCA	431
NM_016286	Reverse Primer	CACTCAGCAGAAAGAGGATGG	432
BC000185	Forward Primer	CATCGAGGACGCTACTTCAAG	433
BC000185	Reverse Primer	AAAATAGGCCTGACGACACCT	434
NM_005505	Forward Primer	TTGGACAACTGGGAAGATTG	435
NM_005505	Reverse Primer	ACGTACTGGGCATAGTGCATC	436
NM_016048	Forward Primer	GGGGATATTATTAGCGTGGGA	437
NM_016048	Reverse Primer	TGCCGCTTCTACTTCTGGTAA	438
BC000195	Forward Primer	TCCACTCACATTTCTATCGG	439
BC000195	Reverse Primer	GATTCCATTTACGGGGAAAAA	440
NM_001306	Forward Primer	AACCTGCATGGACTGTGAAAC	441
NM_001306	Reverse Primer	AATATCAAGTGCCCTTCCAG	442
BC000021	Forward Primer	GCAAGTATAGCGCATTTGAGC	443
BC000021	Reverse Primer	CGTCTTGAAGTCCATGGAGAG	444
W68084	Forward Primer	TTAGATCTGAAGCCCTGGGTT	445
W68084	Reverse Primer	TGCTTGGTGAACATAACACCA	446
AA825563	Forward Primer	AGAAGAAAAACCCAAATGGCA	447
AA825563	Reverse Primer	TCCATAGTGGTTTTTACCAGCA	448
BE887449	Forward Primer	TGCGTACCAGGATTGGTTAAG	449
BE887449	Reverse Primer	GATGTCCAACAAAACGCTCAT	450
AI123815	Forward Primer	TGAGCATGGTATACTTTTGGG	451
AI123815	Reverse Primer	AAGCTTATAGGAATGGGCCAG	452
AI308862	Forward Primer	TGGGAAAATTTAAAACCCACA	453
AI308862	Reverse Primer	TCAAAGTGCCCTTTGGTAGTG	454
AW006352	Forward Primer	TCCTCAAACACAAAATCCCAG	455
AW006352	Reverse Primer	CTCCTACTATGGGCCTCCAAC	456
AL554277	Forward Primer	GAAGCAGATCGTCCTGAACTG	457
AL554277	Reverse Primer	GCTCATCATCCTCTTCTCCCT	458

Genbank Accession No.	RT-PCR Primer Type	Rt-PCR Primer Sequence	SEQ ID NO:
BG289001	Forward Primer	TCCCAATAGCTTGTGGATCAG	459
BG289001	Reverse Primer	ATCAACCAGGAAGCCAACCTTT	460
AI935915	Forward Primer	GACCAACACCTCTCCTAAGGG	461
AI935915	Reverse Primer	GTTGGGAGGGGACCATAGTTA	462
NM_017689	Forward Primer	GAAATAGCAAAAACAAGGCC	463
NM_017689	Reverse Primer	CAATGCAGCACATGCTAGAAA	464
NM_017966	Forward Primer	CAGAATGTAAAGGGTGGGGAT	465
NM_017966	Reverse Primer	CCCTGAGACCTGGTTTACCTC	466
AI923458	Forward Primer	GATGGCAGCTATGAAGTCCTG	467
AI923458	Reverse Primer	GCATTCCAGCTATCACCTGAA	468
NM_000597	Forward Primer	CACCTCTACTCCCTGCACATC	469
NM_000597	Reverse Primer	AGAAGAGATGACACTCGGGGT	470
U90304	Forward Primer	TTTGGCTAAAGACCCGAAAAT	471
U90304	Reverse Primer	TCTCTCTCTCTCGGTGATGGA	472
NM_004968	Forward Primer	GAGCAGGAAAGATGATGCAAG	473
NM_004968	Reverse Primer	AAGTATCTGAGATGGCCCGAT	474
AL563283	Forward Primer	CTCTGGAATGGACTGAAGCTG	475
AL563283	Reverse Primer	AAAAGTCCAGGAGCTGGAGAG	476
AA135522	Forward Primer	CACCTCATCACAACACCCTCT	477
AA135522	Reverse Primer	TGCTAGGATCCACCCTCCTAT	478
AI867102	Forward Primer	CTCTTCCCAGCTCCTGATTCT	479
AI867102	Reverse Primer	CTGAAGGACTGAAGGGAGCTT	480
AW134976	Forward Primer	ACATGCTGTGTGGTAGAGGCT	481
AW134976	Reverse Primer	AACATGCATGCATTGTACCAA	482
AW665865	Forward Primer	TTCCAGGAAGAACATCATTCG	483
AW665865	Reverse Primer	CTTTTCCTTCAGGGAACCAAG	484
AB051487	Forward Primer	TTCTCAGCCAAAGCAGATGTT	485
AB051487	Reverse Primer	TGCTTCTCCTCAGCAATTTGT	486
AB050049	Forward Primer	ACTATGGGATGTGTGGCAGAG	487
AB050049	Reverse Primer	GCTCTTTTAAAGCCGCTTCAT	488
NM_016835	Forward Primer	AAAGAGGCTGACCTTCCAGAG	489
NM_016835	Reverse Primer	AAGGCAAGGCCTATTTTTC	490
AK002075	Forward Primer	GAAGCAATGAATAGCATGGGA	491
AK002075	Reverse Primer	CCATTCCCTCCAGTCACACTGT	492
NM_000933	Forward Primer	TCGGTCTTGGCTACTTGAAGA	493
NM_000933	Reverse Primer	CAGCGTTCCAGAAAATCTGAG	494
NM_012391	Forward Primer	AAGGAGTTGCTACTCAAGCCC	495
NM_012391	Reverse Primer	CTTGTAATACTGGCGGATGGA	496
NM_006443	Forward Primer	CCATCCTTGGGTGTAGGCTAT	497
NM_006443	Reverse Primer	CTCGAAGTATCGATCCAGCAG	498
BC015948	Forward Primer	ATGTGCCCTCACATCTGTTTC	499
BC015948	Reverse Primer	GGGTTTTAACAGCAGGGTAGC	500
AF153330	Forward Primer	GAAATCAGTCTACCAAGGGGC	501
AF153330	Reverse Primer	CGACTTTGCAATCTTGACACA	502
BC002702	Forward Primer	GAAGAGTGGGCAAACATGAAA	503
BC002702	Reverse Primer	CCCACCTGGGAGTAAGTCTTC	504
NM_006416	Forward Primer	CCAGGTGACCTACCAGTTGAA	505
NM_006416	Reverse Primer	TTCCACCACCACTTTTGTAGC	506
NM_030674	Forward Primer	TGGCAAACACTGGAATCCTAC	507
NM_030674	Reverse Primer	TCTGTAGAGAGGTGGCTCCAA	508
AF212371	Forward Primer	CGGATGCTCAGCATCTTCTAC	509
AF212371	Reverse Primer	ACTACCAGGAACAGCAGCAGA	510
AF096304	Forward Primer	AGGCAATCCGATTACGACTT	511

Genbank Accession No.	RT-PCR Primer Type	Rt-PCR Primer Sequence	SEQ ID NO:
AF096304	Reverse Primer	CTCTGCCTCCTTCATCAACAG	512
AK000948	Forward Primer	AGAAGGACTTCTCCAGCAAGG	513
AK000948	Reverse Primer	CTGGGACAGAATGGACAGTGT	514
AI859834	Forward Primer	TGGCCATTTCAGACAGCATTA	515
AI859834	Reverse Primer	CAGCTACTTGGGAGGCTGAG	516
BF512846	Forward Primer	GGGCCCCACTTGACTCATTTA	517
BF512846	Reverse Primer	GCCTGCAGAGATCTCACTTTG	518
NM_022969	Forward Primer	ACAGGATGGGCCTCTCTATGT	519
NM_022969	Reverse Primer	TCCTCAGGAACACGGTTAATG	520
AA741493	Forward Primer	ACACCTTGGTACCACCAATCA	521
AA741493	Reverse Primer	GGTCTCTTGCCCTCATCCAGT	522
NM_001424	Forward Primer	GCATCGCCTTCTTCATCTTC	523
NM_001424	Reverse Primer	CGTAGCTGCCTTCTCTGGTC	524
AW242920	Forward Primer	TTCATGCGTGAAAGTGTGAAG	525
AW242920	Reverse Primer	TTTGATCAAAGGGTGTCTCAG	526
W44413	Forward Primer	GGTAGGGAGCTTCTCAGCAA	527
W44413	Reverse Primer	GTTAGCCCAGAGGAGCTCAA	528
AK021717	Forward Primer	CACAGAAAACACCCCACTT	529
AK021717	Reverse Primer	ACTGTATGGAGGCCCAAGTTG	530

### DETAILED DESCRIPTION OF THE INVENTION

The present invention describes the identification of polynucleotides that correlate with drug sensitivity or resistance of untreated cell lines to determine or predict sensitivity of the cells to a drug, compound, or biological agent. These polynucleotides, called marker or predictor polynucleotides herein, can be employed for predicting drug response. The marker polynucleotides have been determined in an *in vitro* assay employing microarray technology to monitor simultaneously the expression pattern of thousands of discrete polynucleotides in untreated cells, whose sensitivity to compounds or drugs, in particular, compounds that modulate, e.g., inhibit, protein tyrosine kinase or protein tyrosine kinase activity is tested. The protein tyrosine kinases, or activities thereof, associated with response to a drug, compound, or biological agent include, for example, members of the Src family of protein tyrosine kinases, for example, Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as the Bcr-abl, Jak, PDGFR, c-kit and Eph receptors protein tyrosine kinases. (See, e.g., P. Blume-Jensen and T. Hunter, 2001, "Oncopolynucleotide Kinase Signaling", *Nature*, 411:355-365).

The assay according to this invention has allowed the identification of the marker polynucleotides, called protein tyrosine kinase biomarkers herein, having

expression levels in the cells that are highly correlated with drug sensitivity exhibited by the cells. Such marker polynucleotides encompass the above-listed protein tyrosine kinase-encoding polynucleotides, and serve as useful molecular tools for predicting a response to drugs, compounds, biological agents, chemotherapeutic agents, and the like, preferably those drugs and compounds, and the like, that affect protein tyrosine kinase activity via direct or indirect inhibition or antagonism of the protein tyrosine kinase function or activity.

In its preferred aspect, the present invention describes polynucleotides that correlate with sensitivity or resistance of breast cell lines to treatment with a protein tyrosine kinase inhibitor compound, e.g., BMS-A, as described herein. (FIG. 1 and Table 2). The protein tyrosine kinase inhibitor compound, BMS-A, utilized for identifying the polynucleotide predictor sets of this invention, was described in WO 00/62778, published October 26, 2000, and is hereby incorporated by reference in its entirety. BMS-A has potent inhibitory activity for a number of protein tyrosine kinases, for example, members of the Src family of protein tyrosine kinases, including Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as the Bcr-abl, Jak, PDGFR, c-kit and Eph receptors protein tyrosine kinases. Specifically, for the BMS-A protein tyrosine kinase inhibitor compound analyzed, the expression of 137 predictor polynucleotides was found to correlate with resistance/sensitivity of the breast cell lines to the compound.

In accordance with the invention, an approach has been discovered in which polynucleotides and combinations of polynucleotides have been identified whose expression pattern, in a subset of cell lines, correlates to and can be used as an *in vitro* predictor of cellular response to treatment or therapy with one compound, or with a combination or series of compounds, that are known to inhibit or activate the function of a protein, enzyme, or molecule (e.g., a receptor) that is directly or indirectly involved in cell proliferation, cell responses to external stimuli, (such as ligand binding), or signal transduction, e.g., a protein tyrosine kinase. Preferred are antagonists or inhibitors of the function of a given protein, e.g., a tyrosine kinase.

In a preferred aspect, the BMS-A protein tyrosine kinase inhibitor was employed to determine drug sensitivity in a panel of breast cell lines following exposure of the cells to this compound. Some of the cell lines were determined to be

resistant to treatment with the inhibitor compound, while others were determined to be sensitive to the inhibitor. (Table 1). A subset of the cell lines examined provided an expression pattern or profile of polynucleotides, and combinations of polynucleotides, that correlated to, and thus serve as a predictor of, a response by the cells to the inhibitor compound, and to compounds having similar modes of action and/or structure. (Figure 1 and Tables 2 and 4-5).

Such a predictor set of cellular polynucleotide expression patterns correlating with sensitivity or resistance of cells following exposure of the cells to a drug, or a combination of drugs, provides a useful tool for screening a cancer, tumor, or patient test sample before treatment with the drug or a drug combination. The screening technique allows a prediction of cells of a cancer, tumor, or test sample exposed to a drug, or a combination of drugs, based on the polynucleotide expression results of the predictor set, as to whether or not the cancer, tumor, or test sample, and hence a patient harboring the cancer and/or tumor, will or will not respond to treatment with the drug or drug combination. In addition, the predictor polynucleotides or predictor polynucleotide set can also be utilized as described herein for monitoring the progress of disease treatment or therapy in those patients undergoing treatment involving a protein tyrosine kinase, e.g., src tyrosine kinase, inhibitor compound or chemotherapeutic agent for a disease, e.g., breast cancer.

According to a particular embodiment of the present invention, oligonucleotide microarrays were utilized to measure the expression levels of over 44,792 probe sets in a panel of 23 untreated breast cell lines for which the drug sensitivity to the protein tyrosine kinase inhibitor compound was determined. This analysis was performed to determine whether the polynucleotide expression signatures of untreated cells were sufficient for the prediction of chemosensitivity. Data analysis allowed the identification of marker polynucleotides whose expression levels were found to be highly correlated with drug sensitivity. In addition, the treatment of cells with the BMS-A protein tyrosine kinase inhibitor compound also provided polynucleotide expression signatures predictive of sensitivity to the compound. Thus, in one of its embodiments, the present invention provides these polynucleotides, i.e., polynucleotide "markers" or "biomarkers" or "predictors", which show utility in predicting drug response upon treatment or exposure of cells to a drug.

In particular, the marker or predictor polynucleotides are protein tyrosine kinase biomarkers/polynucleotides encoding protein tyrosine kinase biomarker proteins/polypeptides, such as a src tyrosine kinase inhibitor biomarker.

5 The performance of the polynucleotide expression and marker polynucleotide identification analyses embraced by the present invention is described in further detail and without limitation herein below.

#### IC<sub>50</sub> Determination and Phenotype Classification Based on Sensitivity of Twenty-three Breast Cell Lines to Src tyrosine kinase Inhibitor Compounds

20 Twenty-three breast cell lines were treated with a protein tyrosine kinase inhibitor compound (i.e., BMS-A) to determine the individual IC<sub>50</sub> value. The average IC<sub>50</sub> values, along with standard deviations, were calculated from 2 to 5 individual determinations for each cell line. As shown in Table 1, a large variation in the IC<sub>50</sub> values (>1000-fold) was observed for the compound among the twenty-three breast cell lines.

15 The IC<sub>50</sub> value for each cell line was log<sub>10</sub> transformed. The mean of log<sub>10</sub>(IC<sub>50</sub>) across the twenty-three breast cell lines was calculated for the compound. The log<sub>10</sub>(IC<sub>50</sub>) for each cell line was normalized to the mean of log<sub>10</sub>(IC<sub>50</sub>) across the twenty-three breast cell lines for the compound. The cell lines with a log<sub>10</sub>(IC<sub>50</sub>) below the mean of log<sub>10</sub>(IC<sub>50</sub>) were classified as sensitive to the compound, and those  
20 with a log<sub>10</sub>(IC<sub>50</sub>) above the mean of log<sub>10</sub>(IC<sub>50</sub>) were classified as resistant. Table 1 presents the resistance/sensitivity classifications of the twenty-three breast cell lines to the BMS-A compound. As observed in Table 1, seven cell lines were classified as sensitive and sixteen cell lines were classified as resistant to the protein tyrosine kinase inhibitor compound.

#### 25 Identifying Polynucleotides that Significantly Correlated with Drug Resistance/Sensitivity Classification

Expression profiling data of 44,792 probe sets represented on the HG-U133 array set for twenty-three untreated breast cell lines were obtained and preprocessed as described in Example 1, Methods. The preprocessed data containing 5322  
30 polynucleotides were analyzed using K-mean Nearest Neighborhood (KNN) algorithm and "signal to noise model" (T.R. Golub et al., 1999, Science, 286:531-537) to identify polynucleotides whose expression patterns were strongly correlated with



the drug resistance/sensitivity classification (Table 1). An “idealized expression pattern” corresponds to a polynucleotide that is uniformly high in one class (e.g., sensitive) and uniformly low in the other class (e.g., resistant). Initially, a KNN analysis was performed in which a correlation coefficient was obtained for each polynucleotide using “signal to noise model”. The correlation coefficient, which is a measure of relative classification separation, is obtained using the following formula:

$$P(g,c)=(\mu_1 - \mu_2) / (\sigma_1 + \sigma_2).$$

In the above formula, for  $P(g,c)$ ,  $P$  represents correlation coefficient between expression for gene,  $g$ , and the sensitivity/resistance classification,  $c$ ;  $\mu_1$  represents the mean polynucleotide expression level of samples in class 1;  $\mu_2$  represents the mean polynucleotide expression level of samples in class 2;  $\sigma_1$  represents the standard deviation of polynucleotide expression for samples in class 1; and  $\sigma_2$  represents the standard deviation of polynucleotide expression for samples in class 2.

Large values of  $P(g,c)$  indicate a strong correlation between polynucleotide expression and resistance/sensitivity classification. When the correlation is compared to that of a random permutation test (randomly assigned classification), a significance measurement  $p$ -value is obtained. Then, the polynucleotides can be ranked according to the correlation coefficient obtained from this analysis, with the highest value indicating the best correlation of polynucleotide expression level with the resistance/sensitivity classification to the protein tyrosine kinase inhibitor compound in the twenty-three breast cell lines.

The KNN analysis demonstrated that hundreds of polynucleotides correlated to the drug resistance/sensitivity classification for the compound. Therefore, for greater stringency, three different methods were applied to select a smaller subset of polynucleotides that correlated with the drug resistance/sensitive classification for the compound:

First, a permutation test was performed to calculate the significance of the correlation coefficients obtained in the above-described KNN analysis. 350 polynucleotides whose ‘ $p$ ’ value was less than or equal to 0.01 were selected. Second,

the Pearson correlation coefficient (a dimensionless index that ranges from -1.0 to 1.0), was calculated, in which the IC<sub>50</sub> data were considered as a continuous variable and a linear regression model was utilized to correlate polynucleotide expression level with IC<sub>50</sub> values for the twenty-three breast cell lines. Those polynucleotides with a correlation coefficient greater than 0.35 or less than -0.35 were selected (p < 0.05). Finally, Welch t-test was performed, the polynucleotides with p-values equal to or less than 0.05 were selected.

When the three analyses were performed to select polynucleotides correlated with the drug resistance/sensitivity classification for compound BMS-A, the polynucleotide lists from the three analysis methods were obtained and compared. It was observed that there were 168 polynucleotides overlapped from the three analyses. Of these, 32 polynucleotides were redundantly represented more than once on the 168 polynucleotide list, and removed to just leaving one copy per unique gene. Therefore, 137 unique polynucleotides are identified and listed in Table 2. There are 68 polynucleotides highly expressed in the cell lines that were classified as sensitive to BMS-A, while 69 polynucleotides are highly expressed in the cell lines that were classified as resistant to BMS-A. Examples of the polynucleotides include caveolin-1, caveolin-2, and annexin A1 and annexin A2, which are substrates for src tyrosine kinase (M.T. Brown and J.A. Cooper, 1996, *Biochemica et Biophysica Acta*, 1287:121-149). EphA2 and EphB2 are tyrosine kinase receptors, they have diverse roles in carcinopolynucleotidesis (M. Nakamoto and A. D. Bergemann, 2002, *Microscopy Research and Technique* 59:58-67).

#### Identification of polynucleotides modulated by drug treatment

To identify polynucleotides regulated by a protein tyrosine kinase inhibitor compound, e.g., BMS-A, 11 breast cell lines (indicated in bold in the Table 1) having an IC<sub>50</sub> ranging from 0.0055 to 9.5  $\mu$ M were used in a drug treatment study. Cells were treated with or without the BMS-A compound (0.4  $\mu$ M) in 0.1% DMSO for 24 hours. Expression profiling was performed, and the data were analyzed using GeneChip® Expression Analysis software MAS 5.0 (Affymetrix, Santa Clara, CA). The polynucleotide expression of a cell line treated with drug was compared pairwisely to the polynucleotide expression of the same cell line without drug treatment.

A change in p-value was calculated, indicating an increase, decrease or no change in polynucleotide expression. When the p-value was less than 0.0025, the change was considered to be significant. Analysis was performed for all 11 cell lines to compare the polynucleotide expression with and without drug treatment.

5           In addition, a pair-wise t-test with permutation analysis was applied. Polynucleotides that were significantly modulated by the drug treatment in sensitive cell lines and/or in resistant cell lines were identified. Polynucleotides whose expression was significantly changed in at least 3 cell lines were considered to be modulated by the drug. The polynucleotides, whose expression was significantly  
10 correlated with drug resistance/sensitivity classification and modulated by drug treatment as well, are indicated in Table 2. Examples of such polynucleotides include EphA2 and caveolin-2, which were highly expressed in sensitive cells and were down regulated by treatment with the protein tyrosine kinase inhibitor compound BMS-A only in sensitive cell lines as shown in Figure 2.

15           Down regulation of the marker polynucleotides by the protein tyrosine kinase inhibitor compound treatment is also seen in PC3 prostate cell line which is tested to be very sensitive to BMS-A. As illustrated in Figure 3, a dose and time dependent polynucleotide expression decrease of EphA2 and caveolin-2 is observed when compared to the untreated control.

20           Since EphA2 belongs to family of tyrosine kinase receptors, it is possible to test whether cells treated with the protein tyrosine kinase inhibitor compound BMS-A would affect phosphorylation status of EphA2. Immunoblot analysis of protein level and phosphorylation status of EphA2 in nine breast tumor cell lines is shown in Figure 4. Cells were treated with 0.1  $\mu$ M of BMS-A for one hour. Cell lysates were  
25 immuno-precipitated with EphA2 antibody and blot with EphA2 antibody or anti-phosphotyrosine antibody. The results indicate that EphA2 protein level does not change upon the drug treatment for one hour, but the phosphorylation at tyrosine residue is dramatically decreased with the drug treatment. Recombinant human EphA2 protein was also tested in an *in vitro* kinase assay and showed auto  
30 dephosphorylation upon the protein tyrosine kinase inhibitor compound BMS-A treatment with an inhibitory IC<sub>50</sub> of 17 nM.

The identification of those polynucleotides whose expression levels are not only correlated with the sensitivity or resistance of breast cell lines to treatment with a protein tyrosine kinase inhibitor compound (e.g., BMS-A), but also differentially regulated or modified by treatment with the compound can provide additional  
5 information about biological function or activity. The expression levels of these polynucleotides are regulated, or their phosphorylation level is modulated by the inhibitor compound indicating these polynucleotides are likely to be directly or indirectly involved in one or more protein tyrosine kinase signaling pathways, for example, protein tyrosine kinases that are members of the Src family of tyrosine  
10 kinases, including Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as other protein tyrosine kinases, including, Bcr-abl, Jak, PDGFR, c-kit and Eph receptors.

#### Utility of highly correlated polynucleotides to make predictions

Polynucleotides that correlate to a specific property of a biological system can be used to make predictions about that biological system and other biological systems.  
15 The Genecluster software or other programs can be used to select polynucleotides and combinations of polynucleotides that can predict properties using a “weighted-voting cross-validation algorithm” (T.R. Golub et al., 1999, *Science*, 286:531-537). In particular, the Genecluster software was used to build predictors that demonstrate the utility of polynucleotides that correlate to drug sensitivity and resistance. As used  
20 herein, the terms “predictor” or “predictor sets” are used as follows: a predictor or a predictor set refers to a single gene, or combination of polynucleotides, whose expression pattern or properties can be used to make predictions, with different error rates, about a property or characteristic of any given biological system.

The ability of polynucleotide expression patterns to predict a  
25 resistance/sensitive classification was further investigated using a “weighted-voting cross-validation algorithm” which uses a leave one out cross-validation strategy as described by T.R. Golub et al., 1999, *Science*, 286:531-537. The program was formatted to select the optimal number of polynucleotides whose expression pattern could be used to predict, with optimal accuracy, the classification of a cell line based  
30 on resistance or sensitivity toward a given protein tyrosine kinase inhibitor compound, e.g., BMS-A. A brief description of the cross-validation strategy of the program is described.

Based on the leave-one-out cross-validation strategy, a total of twenty-three prediction analyses (i.e., the number of cell lines in the data set) were performed in an iterative manner and the results of all twenty-three prediction analyses were combined to select the optimal number of polynucleotides that had optimal predictive accuracy.

- 5 In each separate prediction analysis, one cell line was withheld from the data set, and an optimal number polynucleotide predictor was built, based on the remaining twenty-two cell lines, and was subsequently used to predict the class of the withheld sample.

Figure 5 shows the real error rates using different numbers of polynucleotides in the predictor set and using different selections and combinations of markers for  
10 predicting classes among the breast cell lines which were either resistant or sensitive to BMS-A. When the predictor sets were selected from the 137 polynucleotides as shown in Table 2, the lowest error rate of 6.3% was achieved in the cross-validation tests with 15 markers. Another predictor set comprised of 7 different polynucleotides selected from the 40 polynucleotides that were modulated by the drug treatment  
15 achieved an error rate of 3.1%. This result indicates that polynucleotides which are not only correlated with drug sensitivity, but also modulated by drug, can provide a better and more accurate prediction in a predictor set.

The real error rates for predicting the sensitivity class of breast cell lines to BMS-A were compared with the real error rates using the same number of  
20 polynucleotides as the predictor set in 20 cases in which classification for the breast cell lines was randomly assigned. As shown in FIG. 6, in the cross-validation tests, when the predictor set contained either 7 or 15 polynucleotides selected from different polynucleotide groups, the error rate for predicting sensitivity of BMS-A in the 23 breast cell lines was 3.1% and 6.3%, respectively. By contrast, the real error rates  
25 ranged from 30% to 83% when using same number of polynucleotides for the predictor set in 20 cases in which classification for the breast cell lines was randomly assigned. This result demonstrated that the error rate value for predicting sensitivity to BMS-A in 23 breast cell lines was significantly lower than the error rate for predicting randomly assigned classification.

30 Table 3 shows the prediction accuracy of the optimal 15 and 7 polynucleotide predictor sets for the resistance/sensitive classification of the twenty-three breast cell lines to BMS-A in the leave-one-out cross validation tests. When a 15 polynucleotide

predictor set selected from the 137 polynucleotides which were derived from above mentioned three analysis methods (i.e., KNN, Pearson correlation between polynucleotide expression level and IC<sub>50</sub> values for the twenty-three breast cell lines, and t-test) was used in a leave-one-out cross-validation test, twenty-one out of twenty-  
5 three samples were correctly predicted and two resistant cell lines, HCC38 and MDA-MB-435S were predicted to be sensitive to BMS-A. This resulted in a 6.3% real error rate, calculated as follows:

$$10 \quad \frac{(2/16 \text{ resistant} + 0/7 \text{ sensitive}) \times 100\%}{2}$$

When a 7 polynucleotide predictor set, selected from the 40 drug treatment modulated polynucleotides that were part of the 137 polynucleotides in Table 2, was used in a leave-one-out cross-validation test, only one resistant cell line, HCC38, was predicted to be sensitive to BMS-A. This resulted in a 3.1% real error rate, calculated  
15 as follows:

$$\frac{(1/16 \text{ resistant} + 0/7 \text{ sensitive}) \times 100\%}{2}$$

20 In addition, a Prediction Strength ("PS") score for each prediction made on a cell line by the predictor set can be obtained from the Genecluster software. The "PS" score ranges from 0 to 1, measuring the margin of victory in each prediction using weighted-voting cross-validation algorithm (see, e.g., T.R. Golub et al., 1999, *Science*, 286:531-537). The higher the value of a PS score is, the more confident the  
25 prediction make. The PS score values for each cell line using the optimal 15 or 7 polynucleotide predictor set, obtained as described above for BMS-A, are shown in Table 3. Note that even though the cell line BT549 was predicted correct to be resistant with both the 15 and 7 polynucleotide predictor sets, the PS score was very low, which means the confidence of prediction is low.

30 It will be appreciated that the exact number of polynucleotides that should comprise an optimal predictor set is not particularly established or defined. It is unlikely in the real world that any predictor set can be obtained with 100% or absolute

accuracy. This is due to the fact that there is a trade-off between the amount of additional information and robustness that are gained by adding more polynucleotides, and the amount of noise that is concomitantly added. In accordance with the present invention, different numbers of polynucleotides were tested in the predictor sets; data  
5 were obtained and analyzed for a protein tyrosine kinase inhibitor, BMS-A. The selection of marker polynucleotides for use in the prediction set was well within the total number of polynucleotides, as shown in Table 2, that strongly correlated with the sensitivity class distinction.

Thus, in accordance with the present invention, an approach has been  
10 developed in which polynucleotides and combinations of polynucleotides have been discovered whose expression pattern in a subset of cell lines correlates with, and can be used as a predictor of, response to treatment with compounds that inhibit the function of protein tyrosine kinases.

Predictor sets, error rates and algorithms used to demonstrate utility

15 The number of polynucleotides in any given predictor or predictor set may influence the error rate of the predictor set in cross validation experiments and with other mathematical algorithms. The data show that the error rate of a predictor is somewhat dependent on the number of polynucleotides in the predictor set and the contribution of each individual polynucleotide in the given predictor set and the  
20 number of cell lines that are tested in the cross validation experiment. For example, in a given predictor set, one polynucleotide may contribute more significantly than other polynucleotides to the prediction.

It is very likely that if a polynucleotide significantly contributes to a predictor set, then it can be used in different combinations with other polynucleotides to  
25 achieve different error rates in different predictor sets. For example, polynucleotide A alone gives an error rate of 30%. In combination with polynucleotides, B, C and D, the error rate becomes 10%; in combination with polynucleotides B, D and E, the error rate becomes 12%; while a combination of polynucleotide A with polynucleotides E-X gives an error rate of 8%, and so on. As demonstrated in FIG. 5,  
30 different selection and combination of polynucleotides in a predictor set achieve different error rates in the cross-validation tests.

When the predictor sets were selected from the 137 polynucleotides as shown in Table 2, the lowest error rate of 6.3% was achieved in the cross-validation test with 15 markers as shown in Table 4. Another predictor set comprised of 7 polynucleotides (Table 5) selected from the 40 polynucleotides that were modulated by the drug treatment, achieved an error rate of 3.1%. This result indicates that polynucleotides which are not only correlated with drug sensitivity, but also modulated by the drug, can provide a better and more accurate prediction in a predictor set.

The error rates as described herein apply to the set of cell lines used in the cross-validation experiment. If a different set is used, or more cell lines are added to the original set tested, then different error rates may be obtained as described and understood by the skilled practitioner. Importantly, different combinations of polynucleotides that correlate to drug sensitivity can be used to build predictors with different prediction accuracy.

#### Expression pattern of the protein tyrosine kinase biomarkers in primary breast tumors

One hundred thirty-four primary breast tumor biopsies were obtained from clinic, and expression profiles of these samples were performed. The expression pattern of the 137 polynucleotides, that are highly correlated with a resistance/sensitivity phenotype classification of the 23 breast cell lines for the protein tyrosine kinase inhibitor compound BMS-A according to the present invention (as shown in FIG.1 and Table 2), were examined in the 134 primary breast tumors as demonstrated in Figure 7. Each row corresponds to a gene, with the columns corresponding to expression level in the different breast tumor samples. The individual polynucleotide encoding the protein tyrosine kinase biomarkers of the invention is in the same order as indicated in Figure 1. It is clear as shown in Figure 7 that a group of primary breast tumors (as indicated by the arrow) highly express the sensitive biomarkers of protein tyrosine kinase inhibitor of the invention. By contrast, another different group primary breast tumors highly express the resistant biomarkers. Although, whether these group of primary breast tumors highly expressing the sensitive biomarkers are really sensitive to the protein tyrosine kinase compounds, e.g., BMS-A is unknown and need to be tested, the fact that the primary breast tumors



exist similar expression pattern of the protein tyrosine kinase biomarkers as the sensitive breast cell lines gives a promise clue.

#### Applications of predictor sets

Predictor sets with different error rates can be used in different applications.

- 5 Predictor sets can be built from any combination of the polynucleotides listed in Table 2, or the predictor polynucleotide subsets of 15 and 7 polynucleotides, as presented in each of Tables 4 and 5, respectively, to make predictions about the likely effect of protein tyrosine modulator compounds, e.g., inhibitors, or compounds that affect a protein tyrosine kinase signaling pathway in different biological systems. The various
- 10 predictor sets described herein, or the combination of these predictor sets with other polynucleotides or other co-variants of these polynucleotides, can have broad utility. For example, the predictor sets can be used as diagnostic or prognostic indicators in disease management; they can be used to predict how patients with cancer might respond to therapeutic intervention with compounds that modulate the protein tyrosine
- 15 kinase family (e.g., the src tyrosine kinase family); and they can be used to predict how patients might respond to therapeutic intervention that modulate signaling through an entire protein tyrosine kinase regulatory pathway, such as, for example, the src tyrosine kinase regulatory pathway.

- 20 While the data described herein were generated in cell lines that are routinely used to screen for and identify compounds that have potential utility for cancer therapy, the predictors can have both diagnostic and prognostic value in other diseases areas in which signaling through a protein tyrosine kinase or a protein tyrosine kinase pathway is of importance, e.g., in immunology, or in cancers or tumors in which cell signaling and/or proliferation controls have gone awry. Such protein tyrosine kinases
- 25 and their pathways comprise, for example, members of the Src family of tyrosine kinases, for example, Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as other protein tyrosine kinases, including, Bcr-abl, Jak, PDGFR, c-kit and Eph receptors. Although the data described herein have been generated using the particularly exemplified protein tyrosine kinase inhibitor compound, BMS-A, three other protein
- 30 tyrosine kinase inhibitor compounds were tested in addition to BMS-A and were found to have similar sensitivity and resistance classifications in the 23 breast cell lines evaluated. Thus, the predictors can have both diagnostic and prognostic value

related to other inhibitor molecules, as well as any molecules or therapeutic interventions that affect protein tyrosine kinases, such as Src tyrosine kinase, or a protein tyrosine kinase signaling pathways, such as that of the Src tyrosine kinase.

Those having skill in the pertinent art will appreciate that protein tyrosine  
5 kinase pathways, e.g., the Src tyrosine kinase pathway, are present and functional in cell types other than cell lines of breast tissue. Therefore, the described predictor set of polynucleotides, or combinations of polynucleotides within the predictor set, can show utility for predicting drug sensitivity or resistance to compounds that interact with, or inhibit, a protein tyrosine kinase activity in cells from other tissues or organs  
10 associated with a disease state, or cancers or tumors derived from other tissue or organ types. Non-limiting examples of such cells, tissues and organs include colon, breast, lung, heart, prostate, testes, ovaries, cervix, esophagus, pancreas, spleen, liver, kidney, intestine, stomach, lymphocytic and brain, thereby providing a broad and advantageous applicability to the predictor polynucleotide sets described herein. Cells  
15 for analysis can be obtained by conventional procedures as known in the art, for example, tissue or organ biopsy, aspiration, sloughed cells, e.g., colonocytes, clinical or medical tissue, or cell sampling procedures.

#### Functionality of polynucleotides that make up a predictor set

The use of a predictor, or predictor set, (e.g., predictor polynucleotides, or a  
20 predictor set of polynucleotides) allows for the prediction of an outcome prior to having any knowledge about a biological system. Essentially, a predictor can be considered to be a tool that is useful in predicting the phenotype that is used to classify the biological system. In the specific embodiment provided by the present invention, the classification as "resistant" or "sensitive" is based on the  $IC_{50}$  value of  
25 each cell line to a compound (e.g., the protein tyrosine kinase inhibitor compound BMS-A as exemplified herein), relative to the mean  $\log_{10}(IC_{50})$  value of the cell line panel (e.g., a twenty-three breast cell line panel, as exemplified herein).

As a particular example, a number of the polynucleotides described herein (Table 2) are known to be substrates for the src tyrosine kinase family, e.g., caveolin-1  
30 and caveolin-2 (M.T. Brown and J.A. Cooper, 1996, *Biochemica et Biophysica Acta*, 1287:121-149). EphA2 is a tyrosine kinase receptor. The data presented herein demonstrated that EphA2 is highly expressed in the sensitive cell lines, and its

expression level and activity are down regulated by treatment of the protein tyrosine kinase inhibitor compound BMS-A. This is expected, since polynucleotides that contribute to a high predictor accuracy are likely to play a functional role in the pathway that is being modulated. For example, Herceptin therapy (i.e., antibody that  
5 binds to the Her2 receptor and prevents function via internalization) is indicated when the Her2 polynucleotide is overexpressed. It is unlikely, although not impossible, that a therapy will have a therapeutic effect if the target enzyme is not expressed.

However, although the complete function of all of the polynucleotides and their functional products (proteins and mRNAs) that make up a predictor set are not  
10 currently known, some of the polynucleotides are likely to be directly or indirectly involved in a protein tyrosine kinase signaling pathway, such as the Src tyrosine kinase signaling pathway. In addition, some of the polynucleotides in the predictor set may function in the metabolic or other resistance pathways specific to the compounds being tested. Notwithstanding, a knowledge about the function of the polynucleotides  
15 is not a requisite for determining the accuracy of a predictor according to the practice of the present invention.

As described herein, polynucleotides have been discovered that correlate to the relative intrinsic sensitivity or resistance of breast cell lines to treatment with compounds that interact with and inhibit protein tyrosine kinases, e.g., Src tyrosine  
20 kinase. These polynucleotides have been shown, through a weighted voting, leave-one-out, cross validation program, to have utility in predicting the intrinsic resistance and sensitivity of breast cell lines to these compounds.

An embodiment of the present invention relates to a method of determining or predicting if an individual requiring drug or chemotherapeutic treatment or therapy for  
25 a disease, for example, a breast cancer or a breast tumor, will be likely to successfully respond or not respond to the drug or chemotherapeutic agent prior to subjecting the individual to such treatment or chemotherapy. The drug or chemotherapeutic agent can be one that modulates a protein tyrosine kinase activity or signaling involving a protein tyrosine kinase. Nonlimiting examples of such protein tyrosine kinases  
30 include members of the Src family of tyrosine kinases, for example, Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as other protein tyrosine kinases, including, Bcr-abl, Jak, PDGFR, c-kit and Eph receptors. In accordance with the method of the

invention, cells from a tissue or organ associated with disease, e.g., a patient biopsy of a tumor or cancer, preferably a breast cancer or tumor biopsy, are subjected to an *in vitro* assay as described herein, to determine their marker polynucleotide expression pattern (polynucleotides from Table 2 and/or the predictor polynucleotide subsets of  
5 Tables 4-5) prior to their treatment with the compound or drug, preferably an inhibitor of a protein tyrosine kinase. The resulting polynucleotide expression profile of the cells before drug treatment is compared with the polynucleotide expression pattern of the same polynucleotides in cells that are either resistant or sensitive to the drug or compound, as provided by the present invention.

10 In another related embodiment, the present invention includes a method of predicting, prognosing, diagnosing, and/or determining whether an individual requiring drug therapy for a disease state or chemotherapeutic for cancer (e.g., breast cancer) will or will not respond to treatment prior to administration of treatment. The treatment or therapy preferably involves a protein tyrosine kinase modulating agent,  
15 compound, or drug, for example, an inhibitor of the protein tyrosine kinase activity. Protein tyrosine kinases include, without limitation, members of the Src family of tyrosine kinases, for example, Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as other protein tyrosine kinases, including, Bcr-abl, Jak, PDGFR, c-kit and Eph receptors. Preferred is src tyrosine kinase and inhibitors thereof. In accordance with  
20 this embodiment, cells from a patient's tissue sample, e.g., a breast tumor or cancer biopsy, are assayed to determine their polynucleotide expression pattern prior to treatment with the protein tyrosine kinase modulating agent, compound, or drug. The resulting polynucleotide expression profile of the test cells before exposure to the compound or drug is compared with that of one or more of the predictor subsets of  
25 polynucleotides comprising either 15 or 7 polynucleotides as described herein and shown in Tables 4-5, respectively.

Success or failure of treatment of a patient's cancer or tumor with the drug can be determined based on the polynucleotide expression pattern of the patient's cells being tested, compared with the polynucleotide expression pattern of the predictor  
30 polynucleotides in the resistant or sensitive panel of that have been exposed to the drug or compound and subjected to the predictor polynucleotide analysis detailed herein. Thus, if following exposure to the drug, the test cells show a polynucleotide

expression pattern corresponding to that of the predictor polynucleotide set of the control panel of cells that is sensitive to the drug or compound, it is highly likely or predicted that the individual's cancer or tumor will respond favorably to treatment with the drug or compound. By contrast, if, after drug exposure, the test cells show a  
5 polynucleotide expression pattern corresponding to that of the predictor polynucleotide set of the control panel of cells that is resistant to the drug or compound, it is highly likely or predicted that the individual's cancer or tumor will not respond to treatment with the drug or compound.

In a related embodiment, screening assays are provided for determining if a  
10 patient's cancer or tumor is or will be susceptible or resistant to treatment with a drug or compound, particularly, a drug or compound directly or indirectly involved in protein tyrosine kinase activity or a protein tyrosine kinase pathway, e.g., the Src tyrosine kinase activity or pathway.

Also provided by the present invention are monitoring assays to monitor the  
15 progress of a drug treatment involving drugs or compounds that interact with or inhibit protein tyrosine kinase activity. Protein tyrosine kinases encompassed by these monitoring assays include members of the Src family of tyrosine kinases, for example, Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as other protein tyrosine kinases, including, Bcr-abl, Jak, PDGFR, c-kit and Eph receptors. Such *in vitro* assays are  
20 capable of monitoring the treatment of a patient having a disease treatable by a compound or agent that modulates or interacts with a protein tyrosine kinase by comparing the resistance or sensitivity polynucleotide expression pattern of cells from a patient tissue sample, e.g., a tumor or cancer biopsy, preferably a breast cancer or tumor sample, prior to treatment with a drug or compound that inhibits the protein  
25 tyrosine kinase activity and again following treatment with the drug or compound with the expression pattern of one or more of the predictor polynucleotide sets described, or combinations thereof. Isolated cells from the patient are assayed to determine their polynucleotide expression pattern before and after exposure to a compound or drug, preferably a protein tyrosine kinase inhibitor, to determine if a  
30 change of the polynucleotide expression profile has occurred so as to warrant treatment with another drug or agent, or discontinuing current treatment. The resulting polynucleotide expression profile of the cells tested before and after

treatment is compared with the polynucleotide expression pattern of the predictor set of polynucleotides that have been described and shown herein to be highly expressed in cells that are either resistant or sensitive to the drug or compound. Alternatively, a patient's progress related to drug treatment or therapy can be monitored by obtaining a polynucleotide expression profile as described above, only after the patient has undergone treatment with a given drug or therapeutic compound. In this way, there is no need to test a patient sample prior to treatment with the drug or compound.

Such a monitoring process can indicate success or failure of a patient's treatment with a drug or compound based on the polynucleotide expression pattern of the cells isolated from the patient's sample, e.g., a tumor or cancer biopsy, as being relatively the same as or different from the polynucleotide expression pattern of the predictor polynucleotide set of the resistant or sensitive control panel of cells that have been exposed to the drug or compound and assessed for their polynucleotide expression profile following exposure. Thus, if, after treatment with a drug or compound, the test cells show a change in their polynucleotide expression profile from that seen prior to treatment to one which corresponds to that of the predictor polynucleotide set of the control panel of cells that are resistant to the drug or compound, it can serve as an indicator that the current treatment should be modified, changed, or even discontinued. Also, should a patient's response be one that shows sensitivity to treatment by a protein tyrosine kinase inhibitor compound, e.g., a Src tyrosine kinase inhibitor, based on correlation of the expression profile of the predictor polynucleotides of cells showing drug sensitivity with the polynucleotide expression profile from cells from a patient undergoing treatment, the patient's treatment prognosis can be qualified as favorable and treatment can continue. Further, if a patient has not been tested prior to drug treatment, the results obtained after treatment can be used to determine the resistance or sensitivity of the cells to the drug based on the polynucleotide expression profile compared with the predictor polynucleotide set.

In a related embodiment, the present invention embraces a method of monitoring the treatment of a patient having a disease treatable by a compound or agent that modulates a protein tyrosine kinase, i.e., breast cancer. Protein tyrosine kinases encompassed by such treatment monitoring assays include members of the Src

family of tyrosine kinases, for example, Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as other protein tyrosine kinases, including, Bcr-abl, Jak, PDGFR, c-kit and Eph receptors. For these assays, test cells from the patient are assayed to determine their polynucleotide expression pattern before and after exposure to a protein tyrosine kinase inhibitor compound or drug. The resulting polynucleotide expression profile of the cells tested before and after treatment is compared with the polynucleotide expression pattern of the predictor set of polynucleotides that have been described and shown herein to be highly expressed in cells that are either resistant or sensitive to the drug or compound. Thus, if a patient's response is or becomes one that is sensitive to treatment by a protein tyrosine kinase inhibitor compound, based on correlation of the expression profile of the predictor polynucleotides, the patient's treatment prognosis can be qualified as favorable and treatment can continue. Also, if after treatment with a drug or compound, the test cells do not exhibit a change in their polynucleotide expression profile to a profile that corresponds to that of the control panel of cells that are sensitive to the drug or compound, this serves as an indicator that the current treatment should be modified, changed, or even discontinued. Such monitoring processes can be repeated as necessary or desired and can indicate success or failure of a patient's treatment with a drug or compound, based on the polynucleotide expression pattern of the cells isolated from the patient's sample. The monitoring of a patient's response to a given drug treatment can also involve testing the patient's cells in the assay as described, only after treatment, rather than before and after treatment, with drug or active compound.

In a preferred embodiment, the present invention embraces a method of monitoring the treatment of a patient having a disease treatable by a compound or agent that modulates a src tyrosine kinase, i.e., breast cancer. The test cells from the patient are assayed to determine their polynucleotide expression pattern before and after exposure to a src tyrosine kinase inhibitor compound or drug. The resulting polynucleotide expression profile of the cells tested before and after treatment is compared with the polynucleotide expression pattern of the predictor set of polynucleotides that have been described and shown herein to be highly expressed in cells that are either resistant or sensitive to the drug or compound. Thus, if a patient's response is or becomes one that is sensitive to treatment by a src tyrosine kinase

inhibitor compound, based on correlation of the expression profile of the predictor polynucleotides, the patient's treatment prognosis can be qualified as favorable and treatment can continue. Also, if after treatment with a drug or compound, the test cells do not exhibit a change in their polynucleotide expression profile to a profile that  
5 corresponds to that of the control panel of cells that are sensitive to the drug or compound, this serves as an indicator that the current treatment should be modified, changed, or even discontinued. Such monitoring processes can be repeated as necessary or desired and can indicate success or failure of a patient's treatment with a drug or compound, based on the polynucleotide expression pattern of the cells isolated  
10 from the patient's sample. The monitoring of a patient's response to a given drug treatment can also involve testing the patient's cells in the assay as described only after treatment, rather than before and after treatment, with drug or active compound.

In another embodiment, the present invention encompasses a method of classifying whether a biological system, preferably cells from a tissue, organ, tumor or  
15 cancer of an afflicted individual, will be resistant or sensitive to a compound that modulates the system. In a preferred aspect of this invention, the sensitivity or resistance of cells, e.g., those obtained from a tumor or cancer, to a protein tyrosine kinase inhibitor compound, or series of compounds, e.g., a Src tyrosine kinase inhibitor, is determined. Inhibitors can include those compounds, drugs, or biological  
20 agents that inhibit, either directly or indirectly, the protein tyrosine kinases as described previously hereinabove. According to the method, a resistance/sensitivity profile of the cells after exposure to the protein tyrosine kinase inhibitor drug or compound can be determined via polynucleotide expression profiling protocols set forth herein. Such resistance/sensitivity profile of the cells reflects an  $IC_{50}$  value of  
25 the cells to the compound(s) as determined using a suitable assay, such as an *in vitro* cytotoxicity assay as described in Example 1. A procedure of this sort can be performed using a variety of cell types and compounds that interact with the protein tyrosine kinase, or affect its activity in the signaling pathway of the protein tyrosine kinase.

30 In another of its embodiments, the present invention includes the preparation of one or more specialized microarrays (e.g., oligonucleotide microarrays or cDNA microarrays) comprising all of the polynucleotides in Tables 2, 4, or 5, or



combinations thereof, of the predictor polynucleotide sets described herein that have been demonstrated to be most highly correlated with sensitivity (or resistance) to protein tyrosine kinase modulators, particularly inhibitors of src tyrosine kinase. Preferably, the predictor polynucleotide sets are common for predicting sensitivity  
5 among more than one protein tyrosine kinase modulator, e.g. a protein tyrosine kinase inhibitor such as a Src tyrosine kinase inhibitor, as demonstrated herein. In accordance with this aspect of the invention, the oligonucleotide sequences or cDNA sequences include any of the predictor polynucleotides or polynucleotide combinations as described herein, which are highly expressed in resistant or sensitive  
10 cells, and are contained on a microarray, e.g., a oligonucleotide microarray or cDNA microarray in association with, or introduced onto, any supporting material, such as glass slides, nylon membrane filters, glass or polymer beads, chips, plates, or other types of suitable substrate material.

Cellular nucleic acid, e.g., RNA, is isolated either from cells undergoing  
15 testing after exposure to a drug or compound that interacts with a protein tyrosine kinase as described herein, or its signaling pathway, or from cells being tested to obtain an initial determination or prediction of the cells' sensitivity to the drug or compound, and, ultimately, a prediction of treatment outcome with the drug or compound. The isolated nucleic acid is appropriately labeled and applied to one or  
20 more of the specialized microarrays. The resulting pattern of polynucleotide expression on the specialized microarray is analyzed as described herein and known in the art. A pattern of polynucleotide expression correlating with either sensitivity or resistance to the drug or compound is able to be determined, e.g., via comparison with the polynucleotide expression pattern as shown in Figure 1 for the panel of cells  
25 exposed to the protein tyrosine kinase inhibitor assayed herein.

In accordance with the specialized microarray embodiment of this invention, the microarray contains the polynucleotides of one or more of the predictor polynucleotide set(s) or subset(s), or a combination thereof, or all of the polynucleotides in Tables 2, 4, or 5, that are highly correlated with drug sensitivity or  
30 resistance by a breast cell type. If the nucleic acid target isolated from test cells, such as tumor or cancer cells, preferably breast cancer or tumor cells, shows a high level of detectable binding to the polynucleotides of the predictor set for drug sensitivity

relative to control, then it can be predicted that a patient's cells will respond to the drug, or a series of drugs, and that the patient's response to the drug, or a series of drugs, will be favorable.

Such a result predicts that the cells of a tumor or cancer are good candidates  
5 for the successful treatment or therapy utilizing the drug, or series of drugs. Alternatively, if the nucleic acid target isolated from test cells shows a high level of detectable binding to the polynucleotides of the predictor set for drug resistance, relative to control, then it can be predicted that a patient is likely not to respond to the drug, or a series of drugs, and that the patient's response to the drug, or a series of  
10 drugs, is not likely to be favorable. Such a result predicts that the cells of a tumor or cancer are not good candidates for treatment or therapy utilizing the drug, or series of drugs.

The utilization of microarray technology is known and practiced in the art. Briefly, to determine polynucleotide expression using microarray technology,  
15 polynucleotides, e.g., RNA, DNA, cDNA, preferably RNA, are isolated from a biological sample, e.g., cells, as described herein for breast cells, using procedures and techniques that are practiced in the art. The isolated nucleic acid is detectably labeled, e.g., fluorescent, enzyme, radionuclide, or chemiluminescent label, and applied to a microarray, e.g., the specialized microarrays provided by this invention. The array is  
20 then washed to remove unbound material and visualized by staining or fluorescence, or other means known in the art depending on the type of label utilized.

In another embodiment of this invention, the predictor polynucleotides (Table 2), or one or more subsets of polynucleotides comprising the predictor polynucleotide sets (e.g., Tables 4-5) can be used as biomarkers for cells that are resistant or sensitive  
25 to protein tyrosine kinase inhibitor compounds, e.g., Src tyrosine kinase inhibitors. With the predictor polynucleotides in hand, screening and detection assays can be carried out to determine whether or not a given compound, preferably a protein tyrosine kinase inhibitor compound such as a Src tyrosine kinase inhibitor compound, elicits a sensitive or a resistant phenotype following exposure of cells, e.g., cells taken  
30 from a tumor or cancer biopsy sample, such as a breast cancer cell sample, to the compound. Thus, methods of screening, monitoring, detecting, prognosing and/or diagnosing to determine the resistance or sensitivity of cells to a drug or compound

that interacts with a protein tyrosine kinase, or a protein tyrosine kinase pathway, preferably an inhibitor compound, and to which the cells are exposed, are encompassed by the present invention.

Such methods embrace a variety of procedures and assays to determine and  
5 assess the expression of polynucleotides, in particular, the predictor or src biomarker polynucleotides and predictor polynucleotide subsets as described herein (Tables 2, 4, and 5), in cells that have been exposed to drugs or compounds that interact with or effect a protein tyrosine kinase, or a protein tyrosine kinase pathway, wherein the protein tyrosine kinases include members of the Src family of tyrosine kinases, for  
10 example, Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as other protein tyrosine kinases, including, Bcr-abl, Jak, PDGFR, c-kit and Eph receptors. Suitable methods include detection and evaluation of polynucleotide activation or expression at the level of nucleic acid, e.g., DNA, RNA, mRNA, and detection and evaluation of encoded protein. For example, PCR assays as known and practiced in the art can be  
15 employed to quantify RNA or DNA in cells being assayed for susceptibility to drug treatment, for example, protein tyrosine kinase inhibitors. (see Example 2, RT-PCR).

In another embodiment, the present invention is directed to a method of identifying cells, tissues, and/or patients that are predicted to be resistant to either protein tyrosine inhibitor compounds or compounds that affect protein tyrosine kinase  
20 signaling pathways, e.g., Src tyrosine kinase, or that are resistant in different biological systems to those compounds. The method comprises the step(s) of (i) analyzing the expression of only those polynucleotides listed in Tables 2, 4, 5, or any combination thereof, that have been shown to be correlative to predicting resistant responses to such compounds; (ii) comparing the observed expression levels of those  
25 correlative resistant polynucleotides in the test cells, tissues, and/or patients to the expression levels of those same polynucleotides in a cell line that is known to be resistant to the compounds; and (iii) predicting whether the cells, tissues, and/or patients are resistant to the compounds based upon the overall similarity of the observed expression of those polynucleotides in step (ii).

30 In another embodiment, the present invention is directed to a method of identifying cells, tissues, and/or patients that are predicted to be sensitive to either protein tyrosine inhibitor compounds or compounds that affect protein tyrosine kinase

signaling pathways, e.g., the Src tyrosine kinase, or that are sensitive in different biological systems to those compounds. The method involves the step(s) of (i) analyzing the expression of only those polynucleotides listed in Tables 2, 4, 5, or any combination thereof, that have been shown to be correlative to predicting sensitive responses to such compounds; (ii) comparing the observed expression levels of those correlative sensitive polynucleotides in the test cells, tissues, and/or patients to the expression levels of those same polynucleotides in a cell line that is known to be sensitive to the compounds; and (iii) predicting whether the cells, tissues, and/or patients are sensitive to the compounds based upon the overall similarity of the observed expression of those polynucleotides in step (ii).

The present invention further encompasses the detection and/or quantification of one or more of the protein tyrosine kinase biomarker proteins of the present invention using antibody-based assays (e.g., immunoassays) and/or detection systems. As mentioned, protein tyrosine kinases encompass members of the Src family of tyrosine kinases, for example, Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as other protein tyrosine kinases, including, Bcr-abl, Jak, PDGFR, c-kit and Eph receptors. Such assays include the following non-limiting examples, ELISA, immunofluorescence, fluorescence activated cell sorting (FACS), Western Blots, etc., as further described herein.

In another embodiment, the human protein tyrosine kinase biomarker polypeptides and/or peptides of the present invention, or immunogenic fragments or oligopeptides thereof, can be used for screening therapeutic drugs or compounds in a variety of drug screening techniques. The fragment employed in such a screening assay can be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The reduction or abolition of activity of the formation of binding complexes between the biomarker protein and the agent being tested can be measured. Thus, the present invention provides a method for screening or assessing a plurality of compounds for their specific binding affinity with a protein kinase inhibitor biomarker polypeptide, or a bindable peptide fragment thereof, of this invention. The method comprises the steps of providing a plurality of compounds; combining the protein kinase inhibitor biomarker polypeptide, or a bindable peptide fragment thereof, with each of the plurality of compounds, for a time sufficient to

allow binding under suitable conditions; and detecting binding of the biomarker polypeptide or peptide to each of the plurality of test compounds, thereby identifying the compounds that specifically bind to the biomarker polypeptide or peptide. More specifically, the biomarker polypeptide or peptide is that of a Src tyrosine kinase inhibitor biomarkers.

Methods to identify compounds that modulate the activity of the human protein tyrosine kinase biomarker polypeptides and/or peptides provided in Table 2 by the present invention, comprise combining a candidate compound or drug modulator of protein kinases and measuring an effect of the candidate compound or drug modulator on the biological activity of the protein kinase inhibitor biomarker polypeptide or peptide. Such measurable effects include, for example, a physical binding interaction; the ability to cleave a suitable protein kinase substrate; effects on a native and cloned protein kinase biomarker-expressing cell line; and effects of modulators or other protein kinase-mediated physiological measures.

Another method of identifying compounds that modulate the biological activity of the protein tyrosine kinase biomarker polypeptides of the present invention comprises combining a potential or candidate compound or drug modulator of a protein tyrosine kinase biological activity, e.g., a Src tyrosine kinase, with a host cell that expresses the protein tyrosine kinase biomarker polypeptide and measuring an effect of the candidate compound or drug modulator on the biological activity of the protein tyrosine kinase biomarker polypeptides. The host cell can also be capable of being induced to express the protein tyrosine kinase biomarker polypeptide, e.g., via inducible expression. Physiological effects of a given modulator candidate on the protein tyrosine kinase biomarker polypeptide can also be measured. Thus, cellular assays for particular protein tyrosine kinase modulators, e.g., a src kinase modulator, can be either direct measurement or quantification of the physical biological activity of the protein tyrosine kinase biomarker polypeptide, or they may be measurement or quantification of a physiological effect. Such methods preferably employ a protein tyrosine kinase biomarker polypeptide as described herein, or an overexpressed recombinant protein tyrosine kinase biomarker polypeptide in suitable host cells containing an expression vector as described herein, wherein the protein tyrosine

kinase biomarker polypeptide is expressed, overexpressed, or undergoes up-regulated expression.

Another aspect of the present invention embraces a method of screening for a compound that is capable of modulating the biological activity of a protein tyrosine kinase biomarker polypeptide, e.g., a Src kinase biomarker polypeptide. The method comprises providing a host cell containing an expression vector harboring a nucleic acid sequence encoding a protein tyrosine kinase biomarker polypeptide, or a functional peptide or portion thereof (e.g., the src polypeptide, protein, peptide, or fragment sequences as set forth in Table 2, or the Sequence Listing herein); determining the biological activity of the expressed protein tyrosine kinase biomarker polypeptide in the absence of a modulator compound; contacting the cell with the modulator compound and determining the biological activity of the expressed protein tyrosine kinase biomarker polypeptide in the presence of the modulator compound. In such a method, a difference between the activity of the protein tyrosine kinase biomarker polypeptide in the presence of the modulator compound and in the absence of the modulator compound indicates a modulating effect of the compound.

Essentially any chemical compound can be employed as a potential modulator or ligand in the assays according to the present invention. Compounds tested as protein tyrosine kinase modulators can be any small chemical compound, or biological entity (e.g., protein, sugar, nucleic acid, or lipid). Test compounds are typically small chemical molecules and peptides. Generally, the compounds used as potential modulators can be dissolved in aqueous or organic (e.g., DMSO-based) solutions. The assays are designed to screen large chemical libraries by automating the assay steps and providing compounds from any convenient source. Assays are typically run in parallel, for example, in microtiter formats on microtiter plates in robotic assays. There are many suppliers of chemical compounds, including, for example, Sigma (St. Louis, MO), Aldrich (St. Louis, MO), Sigma-Aldrich (St. Louis, MO), Fluka Chemika-Biochemica Analytika (Buchs, Switzerland). Also, compounds can be synthesized by methods known in the art.

High throughput screening methodologies are particularly envisioned for the detection of modulators of the novel protein tyrosine kinase biomarker, e.g., src biomarker, polynucleotides and polypeptides described herein. Such high throughput

screening methods typically involve providing a combinatorial chemical or peptide library containing a large number of potential therapeutic compounds (e.g., ligand or modulator compounds). The combinatorial chemical libraries or ligand libraries are then screened in one or more assays to identify those library members (e.g., particular  
5 chemical species or subclasses) that display a desired characteristic activity. The compounds so identified can serve as conventional lead compounds, or can themselves be used as potential or actual therapeutics.

A combinatorial chemical library is a collection of diverse chemical compounds generated either by chemical synthesis or biological synthesis, prepared  
10 by combining a number of chemical building blocks (i.e., reagents such as amino acids). As an example, a linear combinatorial library, e.g., a polypeptide or peptide library, is formed by combining a set of chemical building blocks in every possible way for a given compound length (i.e., the number of amino acids in a polypeptide or peptide compound). Millions of chemical compounds can be synthesized through  
15 such combinatorial mixing of chemical building blocks.

The preparation and screening of combinatorial chemical libraries is well known to those having skill in the pertinent art. Combinatorial libraries include, without limitation, peptide libraries (e.g. U.S. Patent No. 5,010,175; Furka, 1991, *Int. J. Pept. Prot. Res.*, 37:487-493; and Houghton et al., 1991, *Nature*, 354:84-88). Other  
20 chemistries for generating chemical diversity libraries can also be used. Nonlimiting examples of chemical diversity library chemistries include, peptoids (PCT Publication No. WO 91/019735), encoded peptides (PCT Publication No. WO 93/20242), random bio-oligomers (PCT Publication No. WO 92/00091), benzodiazepines (U.S. Patent No. 5,288,514), diversomers such as hydantoins, benzodiazepines and dipeptides  
25 (Hobbs et al., 1993, *Proc. Natl. Acad. Sci. USA*, 90:6909-6913), vinylogous polypeptides (Hagihara et al., 1992, *J. Amer. Chem. Soc.*, 114:6568), nonpeptidal peptidomimetics with glucose scaffolding (Hirschmann et al., 1992, *J. Amer. Chem. Soc.*, 114:9217-9218), analogous organic synthesis of small compound libraries (Chen et al., 1994, *J. Amer. Chem. Soc.*, 116:2661), oligocarbamates (Cho et al., 1993,  
30 *Science*, 261:1303), and/or peptidyl phosphonates (Campbell et al., 1994, *J. Org. Chem.*, 59:658), nucleic acid libraries (see Ausubel, Berger and Sambrook, all supra), peptide nucleic acid libraries (U.S. Patent No. 5,539,083), antibody libraries (e.g.,

Vaughn et al., 1996, *Nature Biotechnology*, 14(3):309-314) and PCT/US96/10287), carbohydrate libraries (e.g., Liang et al., 1996, *Science*, 274-1520-1522) and U.S. Patent No. 5,593,853), small organic molecule libraries (e.g., benzodiazepines, Baum C&EN, Jan. 18, 1993, page 33; and U.S. Patent No. 5,288,514; isoprenoids (U.S. Patent No. 5,569,588); thiazolidinones and metathiazanones (U.S. Patent No. 5,549,974); pyrrolidines (U.S. Patent Nos. 5,525,735 and 5,519,134); morpholino compounds (U.S. Patent No. 5,506,337); and the like.

Devices for the preparation of combinatorial libraries are commercially available (e.g., 357 MPS, 390 MPS, Advanced Chem Tech, Louisville KY; Symphony, Rainin, Woburn, MA; 433A Applied Biosystems, Foster City, CA; 9050 Plus, Millipore, Bedford, MA). In addition, a large number of combinatorial libraries are commercially available (e.g., ComGenex, Princeton, NJ; Asinex, Moscow, Russia; Tripos, Inc., St. Louis, MO; ChemStar, Ltd., Moscow, Russia; 3D Pharmaceuticals, Exton, PA; Martek Biosciences, Columbia, MD, and the like).

In one aspect, the invention provides solid phase-based *in vitro* assays in a high throughput format, where the cell or tissue expressing a tyrosine kinase protein/polypeptide/peptide is attached to a solid phase substrate. In such high throughput assays, it is possible to screen up to several thousand different modulators or ligands in a single day. In particular, each well of a microtiter plate can be used to perform a separate assay against a selected potential modulator, or, if concentration or incubation time effects are to be observed, every 5-10 wells can be used to test a single modulator. Thus, a single standard microtiter plate can be used in to assay about 96 modulators. If 1536 well plates are used, then a single plate can easily assay from about 100 to about 1500 different compounds. It is possible to assay several different plates per day; thus, for example, assay screens for up to about 6,000-20,000 different compounds are possible using the described integrated systems.

In another of its aspects, the present invention encompasses screening and small molecule (e.g., drug) detection assays which involve the detection or identification of small molecules that can bind to a given protein, i.e., a tyrosine kinase biomarker polypeptide or peptide, such as a Src tyrosine kinase biomarker polypeptide or peptide. Particularly preferred are assays suitable for high throughput screening methodologies.



In such binding-based detection, identification, or screening assays, a functional assay is not typically required. All that is needed, in general, is a target protein, preferably substantially purified, and a library or panel of compounds (e.g., ligands, drugs, or small molecules), or biological entities to be screened or assayed for  
5 binding to the protein target. Preferably, most small molecules that bind to the target protein modulate the target's activity in some manner due to preferential, higher affinity binding to functional areas or sites on the protein.

An example of such an assay is the fluorescence based thermal shift assay (3-Dimensional Pharmaceuticals, Inc., 3DP, Exton, PA) as described in U.S. Patent Nos.  
10 6,020,141 and 6,036,920 to Pantoliano et al. (See also, J. Zimmerman, 2000, *Gen. Eng. News*, 20(8)). The assay allows the detection of small molecules (e.g., drugs, ligands) that bind to expressed, and preferably purified, tyrosine kinase biomarker proteins/polypeptides/peptides, such as the Src tyrosine kinase, based on affinity of binding determinations by analyzing thermal unfolding curves of protein-drug or  
15 ligand complexes. The drugs or binding molecules determined by this technique can be further assayed, if desired, by methods such as those described herein to determine if the molecules affect or modulate function or activity of the target protein.

To purify a tyrosine kinase biomarker polypeptide or peptide, e.g., Src tyrosine kinase, to measure a biological binding or ligand binding activity, the source may be a  
20 whole cell lysate that can be prepared by successive freeze-thaw cycles (e.g., one to three) in the presence of standard protease inhibitors. The tyrosine kinase biomarker polypeptide can be partially or completely purified by standard protein purification methods, e.g., affinity chromatography using specific antibody(ies) described herein, or by ligands specific for an epitope tag engineered into the recombinant tyrosine  
25 kinase biomarker polypeptide molecule, also as described herein. Binding activity can then be measured as described.

Compounds which are identified according to the methods provided herein, and which modulate or regulate the biological activity or physiology of the tyrosine kinase biomarker polypeptides according to the present invention, are a preferred  
30 embodiment of this invention. It is contemplated that such modulatory compounds can be employed in treatment and therapeutic methods for treating a condition that is mediated by the tyrosine kinase biomarker polypeptides, e.g., Src tyrosine kinase

biomarker polypeptides, by administering to an individual in need of such treatment a therapeutically effective amount of the compound identified by the methods described herein.

5 In addition, the present invention provides methods for treating an individual in need of such treatment for a disease, disorder, or condition that is mediated by the tyrosine kinase biomarker polypeptides of the invention, comprising administering to the individual a therapeutically effective amount of the tyrosine kinase biomarker-modulating compound identified by a method provided herein. In accordance with this invention, the tyrosine kinase biomarker polypeptides or proteins encompassed by 10 the methods include members of the Src family of tyrosine kinases, for example, Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as other protein tyrosine kinases, including, Bcr-abl, Jak, PDGFR, c-kit and Eph receptors.

The present invention particularly provides methods for treating an individual in need of such treatment for a disease, disorder, or condition that is mediated by Src 15 biomarker polypeptides of the invention, comprising administering to the individual a therapeutically effective amount of the Src biomarker-modulating compound identified by a method provided herein.

The present invention further encompasses polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid 20 sequence of one or more of the protein tyrosine kinase biomarkers, preferably the Src biomarker amino acid sequences as set forth in Table 2. The present invention also encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the protein tyrosine kinase biomarkers of the invention.

The term "epitopes" as used herein, refers to portions of a polypeptide having 25 antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably a human. In a preferred embodiment, the present invention encompasses a polypeptide comprising an epitope, as well as the polynucleotide encoding this polypeptide. An "immunogenic epitope" as used herein, refers to a portion of a protein that elicits an antibody response in an animal, as determined by any method 30 known in the art, for example, by the methods for generating antibodies described *infra*. (See, for example, Geysen et al., 1983, *Proc. Natl. Acad. Sci. USA*, 81:3998-4002). The term "antigenic epitope" as used herein refers to a portion of a protein to

which an antibody can immunospecifically bind to its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding, but does not necessarily exclude cross-reactivity with other antigens. Antigenic epitopes need not necessarily  
5 be immunogenic. Either the full-length protein or an antigenic peptide fragment can be used. Antibodies are preferably prepared from these regions or from discrete fragments in regions of the tyrosine kinase biomarker nucleic acid and protein sequences comprising an epitope. Polypeptide or peptide fragments that function as epitopes may be produced by any conventional means. (See, e.g., Houghten, 1985,  
10 *Proc. Natl. Acad. Sci. USA*, 82:5131-5135; and as described in U. S. Patent No. 4,631,211).

Moreover, antibodies can also be prepared from any region of the polypeptides and peptides of the protein tyrosine kinase biomarkers, including Src kinase biomarkers as described herein. In addition, if a polypeptide is a receptor protein,  
15 antibodies can be developed against an entire receptor or portions of the receptor, for example, the intracellular carboxy terminal domain, the amino terminal extracellular domain, the entire transmembrane domain, specific transmembrane segments, any of the intracellular or extracellular loops, or any portions of these regions. Antibodies can also be developed against specific functional sites, such as the site of ligand  
20 binding, or sites that are glycosylated, phosphorylated, myristylated, or amidated, for example.

In the present invention, antigenic epitopes for generating antibodies preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least  
25 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acid residues. Combinations of the foregoing epitopes are included. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred  
30 antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof, as well as any combination of two, three, four, five or more of these antigenic epitopes. Such antigenic epitopes can be used as the target molecules in

immunoassays. (See, for instance, Wilson et al., 1984, *Cell*, 37:767-778; and Sutcliffe et al., 1983, *Science*, 219:660-666). The fragments as described herein are not to be construed, however, as encompassing any fragments which may be disclosed prior to the invention.

5 Protein tyrosine kinase biomarker polypeptides comprising one or more immunogenic epitopes which elicit an antibody response can be introduced together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse). Alternatively, if the polypeptide is of sufficient length (e.g., at least about 15-25 amino acids), the polypeptide can be presented without a carrier. However,  
10 immunogenic epitopes comprising as few as 5 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

Epitope-bearing polypeptides of the present invention can be used to induce antibodies according to methods well known in the art including, but not limited to, *in vivo* immunization, *in vitro* immunization, and phage display methods. See, e. g.,  
15 Sutcliffe et al., *supra*; Wilson et al., *supra*; and Bittle et al., *supra*). If *in vivo* immunization is used, animals can be immunized with free peptide of appropriate size; however, the anti-peptide antibody titer can be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH), or tetanus toxoid (TT). For instance, peptides containing cysteine residues can be coupled to a  
20 carrier using a linker such as maleimidobenzoyl-N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent, such as glutaraldehyde.

Peptides containing epitopes can also be synthesized as multiple antigen peptides (MAPs), first described by J.P. Tam et al. (1995, *Biomed. Pept., Proteins, Nucleic Acids*, 199, 1(3):123-32) and Calvo et al. (1993, *J. Immunol.*, 150(4):1403-12), which are hereby incorporated by reference in their entirety herein. MAPs contain multiple copies of a specific peptide attached to a non-immunogenic lysine core. MAP peptides usually contain four or eight copies of the peptide, which are  
25 often referred to as MAP4 or MAP8 peptides. By way of non-limiting example, MAPs can be synthesized onto a lysine core matrix attached to a polyethylene glycol-polystyrene (PEG-PS) support. The peptide of interest is synthesized onto the lysine  
30

residues using 9-fluorenylmethoxycarbonyl (Fmoc) chemistry. For example, Applied Biosystems (Foster City, CA) offers commercially available MAP resins, such as, for example, the Fmoc Resin 4 Branch and the Fmoc Resin 8 Branch which can be used to synthesize MAPs. Cleavage of MAPs from the resin is performed with standard trifluoroacetic acid (TFA)-based cocktails known in the art. Purification of MAPs, except for desalting, is not generally necessary. MAP peptides can be used in immunizing vaccines which elicit antibodies that recognize both the MAP and the native protein from which the peptide was derived.

Epitope-bearing peptides of the invention can also be incorporated into a coat protein of a virus, which can then be used as an immunogen or a vaccine with which to immunize animals, including humans, in order stimulate the production of anti-epitope antibodies. For example, the V3 loop of the gp120 glycoprotein of the human immunodeficiency virus type 1 (HIV-1) has been engineered to be expressed on the surface of rhinovirus. Immunization with rhinovirus displaying the V3 loop peptide yielded apparently effective mimics of the HIV-1 immunogens (as measured by their ability to be neutralized by anti-HIV-1 antibodies as well as by their ability to elicit the production of antibodies capable of neutralizing HIV-1 in cell culture). This techniques of using engineered viral particles as immunogens is described in more detail in Smith et al., 1997, *Behring Inst Mitt Feb*, (98):229-39; Smith et al., 1998, *J. Virol.*, 72:651-659; and Zhang et al., 1999, *Biol. Chem.*, 380:365-74), which are hereby incorporated by reference herein in their entirety.

Moreover, polypeptides or peptides containing epitopes according to the present invention can be modified, for example, by the addition of amino acids at the amino- and/or carboxy-terminus of the peptide. Such modifications are performed, for example, to alter the conformation of the epitope bearing polypeptide such that the epitope will have a conformation more closely related to the structure of the epitope in the native protein. An example of a modified epitope-bearing polypeptide of the invention is a polypeptide in which one or more cysteine residues have been added to the polypeptide to allow for the formation of a disulfide bond between two cysteines, thus resulting in a stable loop structure of the epitope-bearing polypeptide under non-reducing conditions. Disulfide bonds can form between a cysteine residue added to the polypeptide and a cysteine residue of the naturally-occurring epitope, or between

two cysteines which have both been added to the naturally-occurring epitope-bearing polypeptide.

In addition, it is possible to modify one or more amino acid residues of the naturally-occurring epitope-bearing polypeptide by substitution with cysteines to promote the formation of disulfide bonded loop structures. Cyclic thioether molecules of synthetic peptides can be routinely generated using techniques known in the art, e.g., as described in PCT publication WO 97/46251, incorporated in its entirety by reference herein. Other modifications of epitope-bearing polypeptides contemplated by this invention include biotinylation.

For the production of antibodies *in vivo*, host animals, such as rabbits, rats, mice, sheep, or goats, are immunized with either free or carrier-coupled peptides or MAP peptides, for example, by intraperitoneal and/or intradermal injection. Injection material is typically an emulsion containing about 100 µg of peptide or carrier protein and Freund's adjuvant, or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal can be increased by selection of anti-peptide antibodies, e.g., by adsorption of the peptide onto a solid support and elution of the selected antibodies according to methods well known in the art.

As one having skill in the art will appreciate, and as discussed above, the tyrosine kinase biomarker polypeptides of the present invention, which include the following: e.g., members of the Src family of tyrosine kinases, such as Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as other protein tyrosine kinases, including, Bcr-abl, Jak, PDGFR, c-kit and Eph receptors, and which comprise an immunogenic or antigenic epitope, can be fused to other polypeptide sequences. For example, the polypeptides of the present invention can be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgD, or IgM), or portions thereof, e.g., CH1, CH2, CH3, or any combination thereof, and portions thereof, or with albumin (including, but not limited to, recombinant human albumin, or fragments or variants thereof (see, e. g., U. S. Patent No. 5,876,969; EP Patent No. 0 413 622; and U.S. Patent No.

5,766,883, incorporated by reference in their entirety herein), thereby resulting in chimeric polypeptides. Such fusion proteins may facilitate purification and may increase half-life *in vivo*. This has been shown for chimeric proteins containing the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (see, e.g.,  
5 Traunecker et al., 1988, *Nature*, 331:84-86).

Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner, such as IgG or Fc fragments (see, e.g., WO 96/22024 and WO  
10 99/04813). IgG fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion disulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than are monomeric polypeptides, or fragments thereof, alone. (See, e.g., Fountoulakis et al., 1995, *J. Biochem.*, 270:3958-3964).

Nucleic acids encoding epitopes can also be recombined with a polynucleotide of interest as an epitope tag (e.g., the hemagglutinin ("HA") tag or flag tag) to aid in  
15 detection and purification of the expressed polypeptide. For example, a system for the ready purification of non-denatured fusion proteins expressed in human cell lines has been described by Janknecht et al., (1991, *Proc. Natl. Acad. Sci. USA*, 88:8972- 897). In this system, the polynucleotide of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the polynucleotide is  
20 translationally fused to an amino-terminal tag having six histidine residues. The tag serves as a matrix binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto an  $\text{Ni}^{2+}$  nitriloacetic acid-agarose column and histidine-tagged proteins are selectively eluted with imidazole-containing  
25 buffers.

Additional fusion proteins of the invention can be generated by employing the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling can be employed to modulate the activities of polypeptides of the invention; such methods can be used to  
30 generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., 1997, *Curr. Opinion Biotechnol.*, 8:724-

33; Harayama, 1998, *Trends Biotechnol.*, 16(2):76-82; Hansson, et al., 1999, *J. Mol. Biol.*, 287:265-76; and Lorenzo and Blasco, 1998, *Biotechniques*, 24(2):308-313, the contents of each of which are hereby incorporated by reference in its entirety.

In an embodiment of the invention, alteration of polynucleotides  
5 corresponding to one or more of the src biomarker polynucleotide sequences as set forth in Table 2, and the polypeptides encoded by these polynucleotides, can be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments by homologous or site-specific recombination to generate variation in the polynucleotide sequence. In another embodiment, polynucleotides of the  
10 invention, or their encoded polypeptides, may be altered by being subjected to random mutapolynucleotidesis by error-prone PCR, random nucleotide insertion, or other methods, prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of this invention may be recombined with one or more components,  
15 motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

Another aspect of the present invention relates to antibodies and T-cell antigen receptors (TCRs), which immunospecifically bind to a polypeptide, polypeptide fragment, or variant one or more of the src biomarker amino acid sequences as set  
20 forth in Table 2, and/or an epitope thereof, of the present invention (as determined by immunoassays well known in the art for assaying specific antibody-antigen binding).

A bispecific or bifunctional antibody is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Bispecific antibodies can be produced by a variety of methods, including fusion of hybridomas or linking of Fab' fragments. (See, e. g., Songsivilai & Lachmann, 1990, *Clin. Exp.*  
25 *Immunol.*, 79:315-321; Kostelny et al., 1992, *J. Immunol.*, 148:1547-1553). In addition, bispecific antibodies can be formed as "diabodies" (See, Holliger et al., 1993, *Proc. Natl. Acad. Sci. USA*, 90:6444-6448), or "Janusins" (See, Traunecker et al., 1991, *EMBO J.*, 10:3655-3659 and Traunecker et al., 1992, *Int. J. Cancer Suppl.*  
30 7:51-52-127).

Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain



antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), intracellularly made antibodies (i.e., intrabodies), and epitope-binding fragments of any of the above. The term "antibody", as used herein,  
5 refers to immunoglobulin molecules and immunologically active portions or fragments of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class or subclass (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) of immunoglobulin  
10 molecule. Preferably, immunoglobulin is an IgG1, an IgG2, or an IgG4 isotype.

Immunoglobulins may have both a heavy and a light chain. An array of IgG, IgE, IgM, IgD, IgA, and IgY heavy chains can be paired with a light chain of the kappa or lambda types. Most preferably, the antibodies of the present invention are human antigen-binding antibodies and antibody fragments and include, but are not  
15 limited to, Fab, Fab' F(ab')<sub>2</sub>, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a V<sub>L</sub> or V<sub>H</sub> domain. Antigen-binding antibody fragments, including single-chain antibodies, can comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, and CH1, CH2, and CH3 domains. Also included in  
20 connection with the invention are antigen-binding fragments comprising any combination of variable region(s) with a hinge region, and CH1, CH2, and CH3 domains. The antibodies of the invention can be from any animal origin including birds and mammals. Preferably, the antibodies are of human, murine (e. g., mouse and rat), donkey, sheep, rabbit, goat, guinea pig, camel, horse, or chicken origin. As  
25 used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from animals transgenic for one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described *infra* and, for example, in U.S. Patent No. 5,939,598.

30 The antibodies of the present invention can be monospecific, bispecific, trispecific, or of greater multispecificity. Multispecific antibodies can be specific for different epitopes of a polypeptide of the present invention, or can be specific for both

a polypeptide of the present invention, and a heterologous epitope, such as a heterologous polypeptide or solid support material. (See, e.g., WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt et al., 1991, *J. Immunol.*, 147:60-69; U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; and  
5 Kostelny et al., 1992, *J. Immunol.*, 148:1547-1553).

Antibodies of the present invention can be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) can be specified, e.g., by N-terminal and C-terminal positions, by size in contiguous amino  
10 acid residues, or as presented in the sequences defined in Table 2 herein. Further included in accordance with the present invention are antibodies which bind to polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under stringent, or moderately stringent, hybridization conditions as described herein.

15 The antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) can bind immunospecifically to a polypeptide or polypeptide fragment or to a variant human protein tyrosine kinase biomarker of the invention, e.g., the Src biomarker proteins as set forth in Table 2, and/or monkey src biomarker protein.

20 By way of non-limiting example, an antibody can be considered to bind to a first antigen preferentially if it binds to the first antigen with a dissociation constant (Kd) that is less than the antibody's Kd for the second antigen. In another non-limiting embodiment, an antibody can be considered to bind to a first antigen preferentially if it binds to the first antigen with an affinity that is at least one order of  
25 magnitude less than the antibody's Ka for the second antigen. In another non-limiting embodiment, an antibody can be considered to bind to a first antigen preferentially if it binds to the first antigen with an affinity that is at least two orders of magnitude less than the antibody's Kd for the second antigen.

In another nonlimiting embodiment, an antibody may be considered to bind to  
30 a first antigen preferentially if it binds to the first antigen with an off rate (koff) that is less than the antibody's koff for the second antigen. In another nonlimiting embodiment, an antibody can be considered to bind to a first antigen preferentially if

it binds to the first antigen with an affinity that is at least one order of magnitude less than the antibody's koff for the second antigen. In another nonlimiting embodiment, an antibody can be considered to bind to a first antigen preferentially if it binds to the first antigen with an affinity that is at least two orders of magnitude less than the antibody's koff for the second antigen.

Antibodies of the present invention can also be described or specified in terms of their binding affinity to a tyrosine kinase biomarker polypeptide of the present invention, e.g., members of the Src family of tyrosine kinases, for example, Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as other protein tyrosine kinases, including, Bcr-abl, Jak, PDGFR, c-kit and Eph receptors. Preferred binding affinities include those with a dissociation constant or Kd of less than  $5 \times 10^{-2}$  M,  $1 \times 10^{-2}$  M,  $5 \times 10^{-3}$  M,  $1 \times 10^{-3}$  M,  $5 \times 10^{-4}$  M, or  $1 \times 10^{-4}$  M. More preferred binding affinities include those with a dissociation constant or Kd less than  $5 \times 10^{-5}$  M,  $1 \times 10^{-5}$  M,  $5 \times 10^{-6}$  M,  $1 \times 10^{-6}$  M,  $5 \times 10^{-7}$  M,  $1 \times 10^{-7}$  M,  $5 \times 10^{-8}$  M, or  $1 \times 10^{-8}$  M. Even more preferred antibody binding affinities include those with a dissociation constant or Kd of less than  $5 \times 10^{-9}$  M,  $1 \times 10^{-9}$  M,  $5 \times 10^{-10}$  M,  $1 \times 10^{-10}$  M,  $5 \times 10^{-11}$  M,  $1 \times 10^{-11}$  M,  $5 \times 10^{-12}$  M,  $1 \times 10^{-12}$  M,  $5 \times 10^{-13}$  M,  $1 \times 10^{-13}$  M,  $5 \times 10^{-14}$  M,  $1 \times 10^{-14}$  M,  $5 \times 10^{-15}$  M, or  $1 \times 10^{-15}$  M.

In specific embodiments, antibodies of the invention bind to the protein tyrosine kinase biomarker polypeptides, or fragments, or variants thereof, with an off rate (koff) of less than or equal to about  $5 \times 10^{-2} \text{ sec}^{-1}$ ,  $1 \times 10^{-2} \text{ sec}^{-1}$ ,  $5 \times 10^{-3} \text{ sec}^{-1}$ , or  $1 \times 10^{-3} \text{ sec}^{-1}$ . More preferably, antibodies of the invention bind to src biomarker protein polypeptides or fragments or variants thereof with an off rate (koff) of less than or equal to about  $5 \times 10^{-4} \text{ sec}^{-1}$ ,  $1 \times 10^{-4} \text{ sec}^{-1}$ ,  $5 \times 10^{-5} \text{ sec}^{-1}$ ,  $1 \times 10^{-5} \text{ sec}^{-1}$ ,  $5 \times 10^{-6} \text{ sec}^{-1}$ ,  $1 \times 10^{-6} \text{ sec}^{-1}$ ,  $5 \times 10^{-7} \text{ sec}^{-1}$ , or  $1 \times 10^{-7} \text{ sec}^{-1}$ .

In other embodiments, antibodies of the invention bind to protein tyrosine kinase biomarker polypeptides or fragments or variants thereof with an on rate (kon) of greater than or equal to  $1 \times 10^3 \text{ M}^{-1} \text{ sec}^{-1}$ ,  $5 \times 10^3 \text{ M}^{-1} \text{ sec}^{-1}$ ,  $1 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$ , or  $5 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$ . More preferably, antibodies of the invention bind to protein tyrosine kinase biomarker polypeptides or fragments or variants thereof with an on rate greater than or equal to  $1 \times 10^5 \text{ M}^{-1} \text{ sec}^{-1}$ ,  $5 \times 10^5 \text{ M}^{-1} \text{ sec}^{-1}$ ,  $1 \times 10^6 \text{ M}^{-1} \text{ sec}^{-1}$ ,  $5 \times 10^6 \text{ M}^{-1} \text{ sec}^{-1}$ , or  $1 \times 10^7 \text{ M}^{-1} \text{ sec}^{-1}$ .

The present invention also provides antibodies that competitively inhibit the binding of an antibody to an epitope of the invention as determined by any method known in the art for determining competitive binding, for example, the immunoassays as described herein. In preferred embodiments, the antibody competitively inhibits  
5 binding to an epitope by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

Antibodies of the present invention can act as agonists or antagonists of the protein tyrosine kinase biomarker polypeptides of the present invention. For example, the present invention includes antibodies which disrupt receptor/ligand interactions  
10 with polypeptides of the invention either partially or fully. The invention includes both receptor-specific antibodies and ligand-specific antibodies. The invention also includes receptor-specific antibodies which do not prevent ligand binding, but do prevent receptor activation. Receptor activation (i.e., signaling) can be determined by techniques described herein or as otherwise known in the art. For example, receptor  
15 activation can be determined by detecting the phosphorylation (e.g., on tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by Western Blot analysis. In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in the  
20 absence of the antibody.

In another embodiment of the present invention, antibodies that immunospecifically bind to a protein tyrosine kinase biomarker, or a fragment or variant thereof, comprise a polypeptide having the amino acid sequence of any one of the heavy chains expressed by an anti-protein tyrosine kinase biomarker antibody-  
25 expressing cell line of the invention, and/or any one of the light chains expressed by an anti-protein tyrosine kinase biomarker antibody-expressing cell line of the invention.

In another embodiment of the present invention, antibodies that immunospecifically bind to a tyrosine kinase biomarker protein or a fragment or  
30 variant thereof, comprise a polypeptide having the amino acid sequence of any one of the V<sub>H</sub> domains of a heavy chain expressed by an anti-protein tyrosine kinase biomarker antibody-expressing cell line, and/or any one of the V<sub>L</sub> domains of a light

chain expressed by an anti-protein tyrosine kinase biomarker antibody-expressing cell line. In preferred embodiments, antibodies of the present invention comprise the amino acid sequence of a  $V_H$  domain and  $V_L$  domain expressed by a single anti-protein tyrosine kinase biomarker protein antibody-expressing cell line. In alternative  
5       embodiments, antibodies of the present invention comprise the amino acid sequence of a  $V_H$  domain and a  $V_L$  domain expressed by two different anti-protein tyrosine kinase biomarker antibody-expressing cell lines.

      Molecules comprising, or alternatively consisting of, antibody fragments or variants of the  $V_H$  and/or  $V_L$  domains expressed by an anti-protein tyrosine kinase  
10       biomarker antibody-expressing cell line that immunospecifically bind to a tyrosine kinase biomarker protein, e.g., Src tyrosine kinase, are also encompassed by the invention, as are nucleic acid molecules encoding these  $V_H$  and  $V_L$  domains, molecules, fragments and/or variants.

      The present invention also provides antibodies that immunospecifically bind  
15       to a polypeptide, or polypeptide fragment or variant of a tyrosine kinase biomarker protein, e.g., a Src kinase biomarker protein, wherein such antibodies comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one, two, three, or more of the  $V_H$  CDRs contained in a heavy chain expressed by one or more anti-tyrosine kinase biomarker protein antibody expressing cell lines. In particular,  
20       the invention provides antibodies that immunospecifically bind to a tyrosine kinase biomarker protein, comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of a  $V_H$  CDR1 contained in a heavy chain expressed by one or more anti-tyrosine kinase biomarker protein antibody expressing cell lines. In another embodiment, antibodies that immunospecifically bind to a tyrosine kinase biomarker  
25       protein, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a  $V_H$  CDR2 contained in a heavy chain expressed by one or more anti-tyrosine kinase biomarker protein antibody expressing cell lines. In a preferred embodiment, antibodies that immunospecifically bind to a tyrosine kinase biomarker protein, comprise, or alternatively consist of, a polypeptide having the amino acid  
30       sequence of a  $V_H$  CDR3 contained in a heavy chain expressed by one or more anti-tyrosine kinase biomarker protein antibody expressing cell line of the invention. Molecules comprising, or alternatively consisting of, these antibodies or antibody

fragments or variants thereof that immunospecifically bind to a tyrosine kinase biomarker protein or a tyrosine kinase biomarker protein fragment or variant thereof are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments and/or variants.

5           The present invention also provides antibodies that immunospecifically bind to a polypeptide, or polypeptide fragment or variant of a tyrosine kinase biomarker protein, e.g., a Src kinase biomarker protein, wherein the antibodies comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one, two, three, or more of the V<sub>L</sub> CDRs contained in a heavy chain expressed by one or more  
10 anti-tyrosine kinase biomarker protein antibody expressing cell lines of the invention. In particular, the invention provides antibodies that immunospecifically bind to a tyrosine kinase biomarker protein, comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of a V<sub>L</sub> CDR1 contained in a heavy chain expressed by one or more anti-tyrosine kinase biomarker protein antibody-expressing  
15 cell lines of the invention. In another embodiment, antibodies that immunospecifically bind to a src biomarker protein, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a V<sub>L</sub> CDR2 contained in a heavy chain expressed by one or more anti-tyrosine kinase biomarker protein antibody-expressing cell lines of the invention. In a preferred embodiment, antibodies that  
20 immunospecifically bind to a tyrosine kinase biomarker protein, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a V<sub>L</sub> CDR3 contained in a heavy chain expressed by one or more anti-tyrosine kinase biomarker protein antibody-expressing cell lines of the invention. Molecules comprising, or alternatively consisting of, these antibodies, or antibody fragments or variants thereof,  
25 that immunospecifically bind to a tyrosine kinase biomarker protein or a tyrosine kinase biomarker protein fragment or variant thereof are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments and/or variants.

          The present invention also provides antibodies (including molecules  
30 comprising, or alternatively consisting of, antibody fragments or variants) that immunospecifically bind to a tyrosine kinase biomarker protein, polypeptide or polypeptide fragment or variant of a tyrosine kinase biomarker protein, e.g., Src

tyrosine kinase, wherein the antibodies comprise, or alternatively consist of, one, two, three, or more  $V_H$  CDRs, and one, two, three or more  $V_L$  CDRs, as contained in a heavy chain or light chain expressed by one or more anti-tyrosine kinase biomarker protein antibody-expressing cell lines of the invention. In particular, the invention provides antibodies that immunospecifically bind to a polypeptide or polypeptide fragment or variant of a tyrosine kinase biomarker protein, wherein the antibodies comprise, or alternatively consist of, a  $V_H$  CDR1 and a  $V_L$  CDR1, a  $V_H$  CDR1 and a  $V_L$  CDR2, a  $V_H$  CDR1 and a  $V_L$  CDR3, a  $V_H$  CDR2 and a  $V_L$  CDR1,  $V_H$  CDR2 and  $V_L$  CDR2, a  $V_H$  CDR2 and a  $V_L$  CDR3, a  $V_H$  CDR3 and a  $V_H$  CDR1, a  $V_H$  CDR3 and a  $V_L$  CDR2, a  $V_H$  CDR3 and a  $V_L$  CDR3, or any combination thereof, of the  $V_H$  CDRs and  $V_L$  CDRs contained in a heavy chain or light chain immunoglobulin molecule expressed by one or more anti-tyrosine kinase biomarker protein antibody-expressing cell lines of the invention. In a preferred embodiment, one or more of these combinations are from a single anti-tyrosine kinase biomarker protein antibody-expressing cell line of the invention. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies that immunospecifically bind to the tyrosine kinase biomarker proteins are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

20        The present invention also provides nucleic acid molecules, generally isolated, encoding an antibody of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof). In a specific embodiment, a nucleic acid molecule of the invention encodes an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), comprising, or alternatively consisting of, a  $V_H$  domain having an amino acid sequence of any one of the  $V_H$  domains of a heavy chain expressed by an anti-tyrosine kinase biomarker protein antibody-expressing cell line of the invention and a  $V_L$  domain having an amino acid sequence of a light chain expressed by an anti-tyrosine kinase biomarker protein antibody-expressing cell line of the invention. In another embodiment, a nucleic acid molecule of the invention encodes an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), comprising, or alternatively consisting of, a  $V_H$  domain having an

amino acid sequence of any one of the V<sub>H</sub> domains of a heavy chain expressed by an anti-tyrosine kinase biomarker protein antibody-expressing cell line of the invention, or a V<sub>L</sub> domain having an amino acid sequence of a light chain expressed by an anti-tyrosine kinase biomarker protein antibody-expressing cell line of the invention.

5           The present invention also provides antibodies that comprise, or alternatively consist of, variants (including derivatives) of the antibody molecules (e.g., the V<sub>H</sub> domains and/or V<sub>L</sub> domains) described herein, which antibodies immunospecifically bind to a tyrosine kinase biomarker protein or fragment or variant thereof, e.g., a Src tyrosine kinase polypeptide.

10           Standard techniques known to those of skill in the art can be used to introduce mutations in the nucleotide sequence encoding a molecule of the invention, including, for example, site-directed mutapolynucleotidesis and PCR-mediated mutapolynucleotidesis which result in amino acid substitutions. Preferably the molecules are immunoglobulin molecules. Also preferably, the variants (including  
15           derivatives) encode less than 50 amino acid substitutions, less than 40 amino acid substitutions, less than 30 amino acid substitutions, less than 25 amino acid substitutions, less than 20 amino acid substitutions, less than 15 amino acid substitutions, less than 10 amino acid substitutions, less than 5 amino acid substitutions, less than 4 amino acid substitutions, less than 3 amino acid  
20           substitutions, or less than 2 amino acid substitutions, relative to the reference V<sub>H</sub> domain, V<sub>H</sub> CDR1, V<sub>H</sub> CDR2, V<sub>H</sub> CDR3, V<sub>L</sub> domain, V<sub>L</sub> CDR1, V<sub>L</sub> CDR2, or V<sub>L</sub> CDR3.

          A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a side chain with a similar  
25           charge. Families of amino acid residues having side chains with similar charges have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine,  
30           proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all



or part of the coding sequence, such as by saturation mutapolynucleotidesis. The resultant mutants can be screened for biological activity to identify mutants that retain activity.

For example, it is possible to introduce mutations only in framework regions  
5 or only in CDR regions of an antibody molecule. Introduced mutations can be silent or neutral missense mutations, i.e., have no, or little, effect on an antibody's ability to bind antigen. These types of mutations can be useful to optimize codon usage, or to improve hybridoma antibody production. Alternatively, non-neutral missense mutations can alter an antibody's ability to bind antigen. The location of most silent  
10 and neutral missense mutations is likely to be in the framework regions, while the location of most non-neutral missense mutations is likely to be in the CDRs, although this is not an absolute requirement. One of skill in the art is able to design and test mutant molecules with desired properties, such as no alteration in antigen binding activity or alteration in binding activity (e.g., improvements in antigen binding  
15 activity or change in antibody specificity). Following mutapolynucleotidesis, the encoded protein may routinely be expressed and the functional and/or biological activity of the encoded protein can be determined using techniques described herein or by routinely modifying techniques known and practiced in the art.

In a specific embodiment, an antibody of the invention (including a molecule  
20 comprising, or alternatively consisting of, an antibody fragment or variant thereof), that immunospecifically binds to protein tyrosine kinase biomarker polypeptides or fragments or variants thereof, comprises, or alternatively consists of, an amino acid sequence encoded by a nucleotide sequence that hybridizes to a nucleotide sequence that is complementary to that encoding one of the  $V_H$  or  $V_L$  domains expressed by one  
25 or more anti-tyrosine kinase biomarker protein antibody-expressing cell lines of the invention, preferably under stringent conditions, e.g., hybridization to filter-bound DNA in 6x sodium chloride/sodium citrate (SSC) at about 45°C followed by one or more washes in 0.2 x SSC/0.1% SDS at about 50°C-65°C, preferably under highly stringent conditions, e.g., hybridization to filter-bound nucleic acid in 6xSSC at about  
30 45°C followed by one or more washes in 0.1xSSC/0.2% SDS at about 68°C, or under other stringent hybridization conditions which are known to those of skill in the art

(see, for example, Ausubel, F.M. et al., eds., 1989, Current Protocols in Molecular Biology, Vol. I, Green Publishing Associates, Inc. and John Wiley & Sons, Inc., New York at pages 6.3.1-6.3.6 and 2.10.3). Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

5           It is well known within the art that polypeptides, or fragments or variants thereof, with similar amino acid sequences often have similar structure and many of the same biological activities. Thus, in one embodiment, an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that immunospecifically binds to a protein tyrosine kinase biomarker  
10 polypeptide or fragments or variants of a tyrosine kinase biomarker polypeptide, comprises, or alternatively consists of, a  $V_H$  domain having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the amino acid sequence of a  $V_H$  domain of a  
15 heavy chain expressed by an anti-tyrosine kinase biomarker protein antibody-expressing cell line of the invention.

          In another embodiment, an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that immunospecifically binds to a tyrosine kinase biomarker polypeptide, or fragments or  
20 variants of a tyrosine kinase biomarker protein polypeptide, comprises, or alternatively consists of, a  $V_L$  domain having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the amino acid sequence of a  $V_L$  domain of a light chain  
25 expressed by an anti-tyrosine kinase biomarker protein antibody-expressing cell line of the invention.

          The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that down-regulate the cell-surface expression of a tyrosine kinase biomarker protein, as  
30 determined by any method known in the art such as, for example, FACS analysis or immunofluorescence assays. By way of a non-limiting hypothesis, such down-regulation can be the result of antibody-induced internalization of a tyrosine kinase

biomarker protein. Such antibodies can comprise, or alternatively consist of, a portion (e. g., V<sub>H</sub> CDR1, V<sub>H</sub> CDR2, V<sub>H</sub> CDR3, V<sub>L</sub> CDR1, V<sub>L</sub> CDR2, or V<sub>L</sub> CDR3) of a V<sub>H</sub> or V<sub>L</sub> domain having an amino acid sequence of an antibody of the invention, or a fragment or variant thereof.

5 In another embodiment, an antibody that down-regulates the cell-surface expression of a tyrosine kinase biomarker protein comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a V<sub>H</sub> domain of an antibody of the invention, or a fragment or variant thereof and a V<sub>L</sub> domain of an antibody of the invention, or a fragment or variant thereof. In another embodiment, an antibody that  
10 down-regulates the cell-surface expression of a tyrosine kinase biomarker protein comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a V<sub>H</sub> domain and a V<sub>L</sub> domain from a single antibody (or scFv or Fab fragment) of the invention, or fragments or variants thereof. In another embodiment, an antibody that down-regulates the cell-surface expression of a tyrosine kinase biomarker protein  
15 comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a V<sub>H</sub> domain of an antibody of the invention, or a fragment or variant thereof. In another embodiment, an antibody that down-regulates the cell-surface expression of a tyrosine kinase biomarker protein comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a V<sub>L</sub> domain of an antibody of the  
20 invention, or a fragment or variant thereof.

In a preferred embodiment, an antibody that down-regulates the cell-surface expression of a tyrosine kinase biomarker protein comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a V<sub>H</sub> CDR3 of an antibody of the invention, or a fragment or variant thereof. In another preferred embodiment, an  
25 antibody that down-regulates the cell-surface expression of a tyrosine kinase biomarker protein comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a V<sub>L</sub> CDR3 of an antibody of the invention, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

30 In another preferred embodiment, an antibody that enhances the activity of a tyrosine kinase biomarker protein, or a fragment or variant thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a V<sub>L</sub> CDR3

of an antibody of the invention, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

As nonlimiting examples, antibodies of the present invention can be used to purify, detect, and target the protein tyrosine kinase polypeptides of the present invention, including both *in vitro* and *in vivo* diagnostic, detection, screening, and/or therapeutic methods. For example, the antibodies have been used in immunoassays for qualitatively and quantitatively measuring levels of src biomarker polypeptides in biological samples. (See, e.g., Harlow et al., *Antibodies : A Laboratory Manual*, Cold Spring Harbor Laboratory Press, 2nd Ed. 1988, which is incorporated by reference herein in its entirety).

By way of another nonlimiting example, antibodies of the invention can be administered to individuals as a form of passive immunization. Alternatively, antibodies of the present invention can be used for epitope mapping to identify the epitope(s) that are bound by the antibody. Epitopes identified in this way can, in turn, for example, be used as vaccine candidates, i.e., to immunize an individual to elicit antibodies against the naturally-occurring forms of one or more tyrosine kinase biomarker proteins.

As discussed in more detail below, the antibodies of the present invention can be used either alone or in combination with other compositions. The antibodies can further be recombinantly fused to a heterologous polypeptide at the N-or C-terminus, or chemically conjugated (including covalent and non-covalent conjugations) to polypeptides or other compositions. For example, antibodies of the present invention can be recombinantly fused or conjugated to molecules that are useful as labels in detection assays and to effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995 and EP 396, 387.

The antibodies of the invention include derivatives that are modified, i.e., by the covalent attachment of any type of molecule to the antibody. For example, without limitation, the antibody derivatives include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications can be

carried out by known techniques, including, but not limited to, specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, and the like. In addition, the antibody derivative can contain one or more non-classical amino acids.

5           The antibodies of the present invention can be generated by any suitable method known in the art. Polyclonal antibodies directed against an antigen or immunogen of interest can be produced by various procedures well known in the art. For example, a tyrosine kinase biomarker polypeptide or peptide of the invention can be administered to various host animals as elucidated above to induce the production  
10   of sera containing polyclonal antibodies specific for the biomarker antigen. Various adjuvants can also be used to increase the immunological response, depending on the host species; adjuvants include, but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet  
15   hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

Monoclonal antibodies can be prepared using a wide variety of techniques known in the art, including the use of hybridoma, recombinant and phage display  
20   technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques as known and practiced in the art and as taught, for example, in Kohler and Milstein, 1975, *Nature*, 256:495-497; Harlow et al., *Antibodies : A Laboratory Manual*, Cold Spring Harbor Laboratory Press, 2nd Ed. 1988; and Hammerling, et al., In: *Monoclonal Antibodies and T-Cell Hybridomas*,  
25   Elsevier, N. Y., pages 563-681, 1981, the contents of which are incorporated herein by reference in their entireties. The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and does not necessarily refer to the method  
30   by which it is produced. Techniques involving continuous cell line cultures can also be used. In addition to the hybridoma technique, other techniques include the trioma technique, the human B-cell hybridoma technique (Kozbor et al., 1983, *Immunol.*

Today, 4:72), and the EBV-hybridoma technique (Cole et al., 1985. In: *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96).

Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art. As a nonlimiting example, mice can  
5 be immunized with a tyrosine kinase polypeptide or peptide of the invention, or variant thereof, or with a cell expressing the polypeptide or peptide or variant thereof. Once an immune response is detected, e.g., antibodies specific for the antigen are detected in the sera of immunized mice, the spleen is harvested and splenocytes are isolated. The splenocytes are then fused by well known techniques to any suitable  
10 myeloma cells, for example cells from cell line SP2/0 or P3X63-AG8.653 available from the ATCC. Hybridomas are selected and cloned by limiting dilution techniques. The hybridoma clones are then assayed by methods known in the art to determine and select those cells that secrete antibodies capable of binding to a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be  
15 generated by immunizing mice with positive hybridoma clones.

Another well known method for producing both polyclonal and monoclonal human B cell lines is transformation using Epstein Barr Virus (EBV). Protocols for generating EBV-transformed B cell lines are commonly known in the art, such as, for example, the protocol outlined in Chapter 7.22 of *Current Protocols in Immunology*,  
20 Coligan et al., Eds., 1994, John Wiley & Sons, NY, which is hereby incorporated by reference herein in its entirety. The source of B cells for transformation is commonly human peripheral blood, but B cells for transformation can also be obtained from other sources including, but not limited to, lymph node, tonsil, spleen, tumor tissue, and infected tissues. Tissues are generally prepared as single cell suspensions prior to  
25 EBV transformation. In addition, T cells that may be present in the B cell samples can be either physically removed or inactivated (e.g., by treatment with cyclosporin A). The removal of T cells is often advantageous, because T cells from individuals seropositive for anti-EBV antibodies can suppress B cell immortalization by EBV. In general, a sample containing human B cells is inoculated with EBV and cultured for  
30 3-4 weeks. A typical source of EBV is the culture supernatant of the B95-8 cell line (ATCC; VR-1492). Physical signs of EBV transformation can generally be seen toward the end of the 3-4 week culture period.

By phase-contrast microscopy, transformed cells appear large, clear and "hairy"; they tend to aggregate in tight clusters of cells. Initially, EBV lines are generally polyclonal. However, over prolonged periods of cell culture, EBV lines can become monoclonal as a result of the selective outgrowth of particular B cell clones.

5 Alternatively, polyclonal EBV transformed lines can be subcloned (e.g., by limiting dilution) or fused with a suitable fusion partner and plated at limiting dilution to obtain monoclonal B cell lines. Suitable fusion partners for EBV transformed cell lines include mouse myeloma cell lines (e.g., SP2/0, X63-Ag8.653), heteromyeloma cell lines (human x mouse ; e.g., SPAM-8, SBC-H20, and CB-F7), and human cell

10 lines (e.g., GM 1500, SKO-007, RPMI 8226, and KR-4). Thus, the present invention also includes a method of generating polyclonal or monoclonal human antibodies against protein tyrosine kinase polypeptides and peptides of the invention, or fragments thereof, comprising EBV-transformation of human B cells.

Antibody fragments that recognize specific epitopes can be generated by

15 known techniques. For example, Fab and F(ab')<sub>2</sub> fragments of the invention can be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F (ab')<sub>2</sub> fragments). F(ab')<sub>2</sub> fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain.

20 Antibodies encompassed by the present invention can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or

25 combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds to the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured onto a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv, or disulfide stabilized

30 antibody domains recombinantly fused to either the phage polynucleotide III or polynucleotide VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et

al., 1995, *J. Immunol. Methods*, 182:41-50; Ames et al., 1995, *J. Immunol. Methods*, 184:177-186; Kettleborough et al., 1994, *Eur. J. Immunol.*, 24:952-958; Persic et al., 1997, *Gene*, 187:9-18; Burton et al., 1994, *Advances in Immunology*, 57:191-280; PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO  
5 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108, each of which is incorporated herein by reference in its entirety.

10 As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below.

15 Examples of techniques that can be used to produce single-chain Fvs and antibodies include those described in U.S. Patent Nos. 4,946,778 and 5,258,498; Huston et al., 1991, *Methods in Enzymology*, 203:46-88; Shu et al., 1993, *Proc. Natl. Acad. Sci. USA*, 90:7995-7999; and Skerra et al., 1988, *Science*, 240:1038-1040. For some uses, including the *in vivo* use of antibodies in humans and in *in vitro* detection  
20 assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal immunoglobulin and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art.  
25 (See, e.g., Morrison, 1985, *Science*, 229:1202; Oi et al., 1986, *BioTechniques*, 4:214; Gillies et al., 1989, *J. Immunol. Methods*, 125:191-202; and U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entirety).

Humanized antibodies are antibody molecules from non-human species that  
30 bind to the desired antigen and have one or more complementarity determining regions (CDRs) from the nonhuman species and framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework



regions are substituted with corresponding residues from the CDR and framework regions of the donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify  
5 framework residues important for antigen binding, and by sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent Nos. 5,693,762 and 5,585,089; and Riechmann et al., 1988, *Nature*, 332:323, which are incorporated herein by reference in their entireties). Antibodies can be humanized using a variety of techniques known in the art, including, for  
10 example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089); veneering or resurfacing (EP 592,106; EP 519,596; Padlan, 1991, *Molecular Immunology*, 28(4/5):489-498; Studnicka et al., 1994, *Protein Engineering*, 7(6):805-814; Roguska et al., 1994, *Proc. Natl. Acad. Sci. USA*, 91:969-973; and chain shuffling (U.S. Patent No. 5,565,332).

15 Completely human antibodies can be made by a variety of methods known in the art, including the phage display methods described above, using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of  
20 which is incorporated herein by reference in its entirety.

Completely human antibodies are particularly desirable for therapeutic treatment of human patients, so as to avoid or alleviate immune reaction to foreign protein. Human antibodies can be made by a variety of methods known in the art, including the phage display methods described above, using antibody libraries derived  
25 from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

Human antibodies can also be produced using transgenic mice which are  
30 incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin polynucleotides. For example, the human heavy and light chain immunoglobulin polynucleotide complexes can be introduced randomly,

or by homologous recombination, into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells, in addition to the human heavy and light chain polynucleotides. The mouse heavy and light chain immunoglobulin polynucleotides can be rendered nonfunctional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the J<sub>H</sub> region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention.

Thus, using such a technique, it is possible to produce useful human IgG, IgA, IgM, IgD and IgE antibodies. For an overview of the technology for producing human antibodies, see Lonberg and Huszar, 1995, *Intl. Rev. Immunol.*, 13:65-93. For a detailed discussion of the technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; 5,939,598; 6,075,181; and 6,114,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Fremont, CA), Protein Design Labs, Inc. (Mountain View, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to the above described technologies.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection". In this approach, a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., 1988, *BioTechnology*, 12:899-903).

Further, antibodies to the protein tyrosine kinase polypeptides of the invention can, in turn, be utilized to generate anti-idiotypic antibodies that "mimic" protein

tyrosine kinase biomarker polypeptides of the invention using techniques well known to those skilled in the art. (See, e.g., Greenspan and Bona, 1989, *FASEB J.*, 7(5):437-444 and Nissinoff, 1991, *J. Immunol.*, 147(8):2429-2438). For example, antibodies which bind to and competitively inhibit polypeptide multimerization and/or binding of  
5 a polypeptide of the invention to a ligand can be used to generate anti-idiotypes that "mimic" the polypeptide multimerization and/or binding domain and, as a consequence, bind to and neutralize the polypeptide and/or its ligand, e.g., in therapeutic regimens. Such neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used to neutralize polypeptide ligand. For example, such anti-  
10 idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligands/receptors, and thereby activate or block its biological activity.

Intrabodies are antibodies, often scFvs, that are expressed from a recombinant nucleic acid molecule and are engineered to be retained intracellularly (e.g., retained in the cytoplasm, endoplasmic reticulum, or periplasm of the host cells). Intrabodies  
15 can be used, for example, to ablate the function of a protein to which the intrabody binds. The expression of intrabodies can also be regulated through the use of inducible promoters in the nucleic acid expression vector comprising nucleic acid encoding the intrabody. Intrabodies of the invention can be produced using methods known in the art, such as those disclosed and reviewed in Chen et al., 1994, *Hum.*  
20 *Polynucleotide Ther.*, 5:595-601; Marasco, W.A., 1997, *Polynucleotide Ther.*, 4:11-15; Rondon and Marasco, 1997, *Annu. Rev. Microbiol.*, 51:257-283; Proba et al., 1998, *J. Mol. Biol.*, 275:245-253; Cohen et al., 1998, *Oncogene*, 17:2445-2456; Ohage and Steipe, 1999, *J. Mol. Biol.*, 291:1119-1128; Ohage et al., 1999, *J. Mol. Biol.*, 291:1129-1134; Wirtz and Steipe, 1999, *Protein Sci.*, 8:2245-2250; and Zhu et  
25 al., 1999, *J. Immunol. Methods*, 231:207-222.

XenoMouse Technology Antibodies in accordance with the invention are preferably prepared by the utilization of a transgenic mouse that has a substantial portion of the human antibody producing genome inserted into its genome, but that is rendered deficient in the production of endogenous murine antibodies (e.g.,  
30 XenoMouse strains available from Abgenix Inc., Fremont, CA). Such mice are capable of producing human immunoglobulin molecules and are virtually deficient in the production of murine immunoglobulin molecules. Technologies utilized for

achieving the same are disclosed in the patents, applications, and references disclosed herein.

The ability to clone and reconstruct megabase-sized human loci in YACs and to introduce them into the mouse germline provides a powerful approach to elucidating the functional components of very large or crudely mapped loci, as well as generating useful models of human disease. Furthermore, the utilization of such technology for substitution of mouse loci with their human equivalents could provide unique insights into the expression and regulation of human polynucleotide products during development, their communication with other systems, and their involvement in disease induction and progression. An important practical application of such a strategy is the "humanization" of the mouse humoral immune system. Introduction of human immunoglobulin (Ig) loci into mice in which the endogenous Ig polynucleotides have been inactivated offers the opportunity to study the mechanisms underlying programmed expression and assembly of antibodies as well as their role in B cell development. Furthermore, such a strategy could provide an ideal source for the production of fully human monoclonal antibodies (Mabs), which is an important milestone toward fulfilling the promise of antibody therapy in human disease.

Fully human antibodies are expected to minimize the immunogenic and allergic responses intrinsic to mouse or mouse-derivatized monoclonal antibodies and thus to increase the efficacy and safety of the administered antibodies. The use of fully human antibodies can be expected to provide a substantial advantage in the treatment of chronic and recurring human diseases, such as cancer, which require repeated antibody administrations.

One approach toward this goal was to engineer mouse strains deficient in mouse antibody production to harbor large fragments of the human Ig loci in anticipation that such mice would produce a large repertoire of human antibodies in the absence of mouse antibodies. Large human Ig fragments would preserve the large variable polynucleotide diversity as well as the proper regulation of antibody production and expression. By exploiting the mouse machinery for antibody diversification and selection and the lack of immunological tolerance to human proteins, the reproduced human antibody repertoire in these mouse strains should yield high affinity antibodies against any antigen of interest, including human

antigens. Using the hybridoma technology, antigen-specific human monoclonal antibodies with the desired specificity could be readily produced and selected.

This general strategy was demonstrated in connection with the generation of the first "XenoMouseT" strains as published in 1994. See Green et al., 1994, *Nature Genetics*, 7:13-21. The XenoMouse strains were engineered with yeast artificial chromosomes (YACS) containing 245 kb and 10, 190 kb-sized germline configuration fragments of the human heavy chain locus and kappa light chain locus, respectively, which contained core variable and constant region sequences. *Id.* The human Ig-containing YACs proved to be compatible with the mouse system for both rearrangement and expression of antibodies and were capable of substituting for the inactivated mouse Ig polynucleotides. This was demonstrated by their ability to induce B-cell development, to produce an adult-like human repertoire of fully human antibodies, and to generate antigen-specific human monoclonal antibodies. These results also suggested that introduction of larger portions of the human Ig loci containing greater numbers of V polynucleotides, additional regulatory elements, and human Ig constant regions might recapitulate substantially the full repertoire that is characteristic of the human humoral response to infection and immunization. The work of Green et al. was recently extended to the introduction of greater than approximately 80% of the human antibody repertoire through the use of megabase-sized, germline configuration YAC fragments of the human heavy chain loci and kappa light chain loci, respectively, to produce XenoMouse mice. See Mendez et al., 1997, *Nature Genetics*, 15:146-156; Green and Jakobovits, 1998, *J. Exp. Med.*, 188:483-495; and Green, 1999, *Journal of Immunological Methods*, 231:11-23, the disclosures of which are hereby incorporated herein by reference.

Human anti-mouse antibody (HAMA) responses have led the industry to prepare chimeric or otherwise humanized antibodies. While chimeric antibodies typically are comprised of a human constant region and a murine variable region, it is expected that certain human anti-chimeric antibody (HACA) responses will be observed, particularly in treatments involving chronic or multi-dose utilizations of the antibody. Thus, it is desirable to provide fully human antibodies against protein tyrosine kinase biomarker polypeptides in order to vitiate concerns and/or effects of HAMA or HACA responses.

Antibodies of the invention can be chemically synthesized or produced through the use of recombinant expression systems. Accordingly, the invention further embraces polynucleotides comprising a nucleotide sequence encoding an antibody of the invention and fragments thereof. The invention also encompasses  
5 polynucleotides that hybridize under stringent or lower stringency hybridization conditions, e.g., as defined supra, to polynucleotides that encode an antibody, preferably, an antibody that specifically binds to a protein tyrosine kinase polypeptide of this invention, and more preferably, an antibody that binds to a polypeptide having the amino acid sequence of one or more of the protein tyrosine kinase biomarker  
10 sequences, e.g., Src tyrosine kinase biomarkers, as set forth in Table 2.

The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody can be assembled from chemically synthesized oligonucleotides (e.g., as described in  
15 Kutmeier et al., 1994, *BioTechniques*, 17:242), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, the annealing and ligating of those oligonucleotides, and then the amplification of the ligated oligonucleotides by PCR.

Alternatively, a polynucleotide encoding an antibody can be generated from  
20 nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin can be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, (or a nucleic acid, preferably poly A+ RNA, isolated from), any tissue  
25 or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence. Alternatively, cloning using an oligonucleotide probe specific for the particular polynucleotide sequence to be identified, e.g., a cDNA clone from a cDNA library that encodes the desired antibody can be employed.  
30 Amplified nucleic acids generated by PCR can then be cloned into replicable cloning vectors using any method well known in the art.

Once the nucleotide sequence and corresponding encoded amino acid sequence of the antibody are determined, the nucleotide sequence of the antibody can be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutapolynucleotidesis, PCR, etc. (see, for example, the techniques described in  
5 Sambrook et al., 1990, *Molecular Cloning, A Laboratory Manual*, 2nd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY; and F.M. Ausubel et al., eds., 1998, *Current Protocols in Molecular Biology*, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having  
10 a different amino acid sequence, for example, to create amino acid substitutions, deletions, and/or insertions.

In a specific embodiment, the amino acid sequence of the heavy and/or light chain variable domains can be inspected to identify the sequences of the CDRs by methods that are well known in the art, e.g., by comparison to known amino acid  
15 sequences of other heavy and light chain variable regions, to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs can be inserted within framework regions, e.g., into human framework regions, to humanize a non-human antibody, as described *supra*. The framework regions can be naturally occurring or consensus framework regions, and preferably,  
20 are human framework regions (see, e.g., Chothia et al., 1998, *J. Mol. Biol.*, 278:457-479, for a listing of human framework regions).

Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds to a protein tyrosine kinase biomarker polypeptide of the invention. Also preferably, as discussed *supra*,  
25 one or more amino acid substitutions can be made within the framework regions; such amino acid substitutions are performed with the goal of improving binding of the antibody to its antigen, e.g., greater antibody binding affinity. In addition, such methods can be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to  
30 generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations that can be made to the polynucleotide are encompassed by the present invention and are within the skill of the art.

For some uses, such as for *in vitro* affinity maturation of an antibody of the invention, it is useful to express the V<sub>H</sub> and V<sub>L</sub> domains of the heavy and light chains of one or more antibodies of the invention as single chain antibodies, or Fab fragments, in a phage display library using phage display methods as described *supra*.

- 5 For example, the cDNAs encoding the V<sub>H</sub> and V<sub>L</sub> domains of one or more antibodies of the invention can be expressed in all possible combinations using a phage display library, thereby allowing for the selection of V<sub>H</sub>/V<sub>L</sub> combinations that bind to the protein tyrosine kinase biomarker polypeptides according to the present invention with preferred binding characteristics such as improved affinity or improved off rates.
- 10 In addition, V<sub>H</sub> and V<sub>L</sub> segments, particularly, the CDR regions of the V<sub>H</sub> and V<sub>L</sub> domains of one or more antibodies of the invention, can be mutated *in vitro*. Expression of V<sub>H</sub> and V<sub>L</sub> domains with "mutant" CDRs in a phage display library allows for the selection of V<sub>H</sub>/V<sub>L</sub> combinations that bind to protein tyrosine kinase biomarkers, e.g., Src tyrosine kinase biomarker proteins, which are receptor
- 15 polypeptides with preferred binding characteristics such as improved affinity or improved off rates.

- Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it can be purified by any method known in the art for the purification of an immunoglobulin or polypeptide molecule,
- 20 for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen, Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous polypeptide sequences described
- 25 herein or otherwise known in the art, to facilitate purification.

- The present invention encompasses antibodies that are recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugated) to a polypeptide (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention to generate fusion
- 30 proteins. The fusion does not necessarily need to be direct, but can occur through linker sequences. The antibodies can be specific for antigens other than polypeptides (or portions thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino



acids of the polypeptide) of the present invention. For example, antibodies can be used to target the polypeptides of the present invention to particular cell types, either *in vitro* or *in vivo*, by fusing or conjugating the polypeptides of the present invention to antibodies specific for particular cell surface receptors.

5           The present invention further includes compositions comprising the protein tyrosine kinase biomarker polypeptides of the present invention fused or conjugated to antibody domains other than the variable region domain. For example, the polypeptides of the present invention can be fused or conjugated to an antibody Fc region, or portion thereof. The antibody portion fused to a polypeptide of the present  
10 invention can comprise the constant region, hinge region, CH1 domain, CH2 domain, CH3 domain, or any combination of whole domains or portions thereof. The polypeptides can also be fused or conjugated to the above antibody portions to form multimers. For example, Fc portions of immunoglobulin molecules fused to the polypeptides of the present invention can form dimers through disulfide bonding  
15 between the Fc portions. Higher multimeric forms can be made by fusing the polypeptides to portions of IgA and IgM. Methods for fusing or conjugating the polypeptides of the present invention to antibody portions are known in the art. (See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., 1991, *Proc. Natl. Acad. Sci. USA*, 88:10535-10539; Zheng et al.,  
20 1995, *J. Immunol.*, 154:5590-5600; and Vil et al., *Proc. Natl. Acad. Sci. USA*, 89:11337-11341, which are hereby incorporated by reference herein in their entireties).

As discussed *supra*, the polypeptides corresponding to a polypeptide,  
25 polypeptide fragment, or a variant of one or more of the protein tyrosine kinase biomarker amino acid sequences as set forth in Table 2 can be fused or conjugated to the above antibody portions to increase the *in vivo* half life of the polypeptides, or for use in immunoassays using methods known in the art. Further, the polypeptides corresponding to one or more of the protein tyrosine kinase biomarker, e.g., src  
30 biomarker, sequences as set forth in Table 2 can be fused or conjugated to the above antibody portions to facilitate purification. For guidance, chimeric proteins having the first two domains of the human CD4 polypeptide and various domains of the constant

regions of the heavy or light chains of mammalian immunoglobulins have been described. (EP 394,827; Traunecker et al., 1988, *Nature*, 331:84-86). The polypeptides of the present invention fused or conjugated to an antibody, or portion thereof, having disulfide-linked dimeric structures (due to the IgG), for example, can also be more efficient in binding and neutralizing other molecules than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., 1995, *J. Biochem.*, 270:3958-3964). In many cases, the Fc portion in a fusion protein is beneficial in therapy, diagnosis, and/or screening methods, and thus can result in, for example, improved pharmacokinetic properties. (EP 232, 262 A). In drug discovery, for example, human proteins, such as huIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of huIL-5. (See, Bennett et al., 1995, *J. Molecular Recognition*, 8:52-58; and Johanson et al., 1995, *J. Biol. Chem.*, 270:9459-9471). Alternatively, deleting the Fc portion after the fusion protein has been expressed, detected, and purified may be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations.

Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide, to facilitate their purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., Chatsworth, CA), among others, many of which are commercially available. As described in Gentz et al., 1989, *Proc. Natl. Acad. Sci. USA*, 86:821-824, for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin (HA) protein (Wilson et al., 1984, *Cell*, 37:767) and the "flag" tag.

The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure, for example, to determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Nonlimiting examples of detectable substances include various

enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance can be coupled or conjugated either directly to the antibody  
5 (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. (See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention).

Nonlimiting examples of suitable enzymes include horseradish peroxidase,  
10 alkaline phosphatase, beta-galactosidase, or acetylcholinesterase. Nonlimiting examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; nonlimiting examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; a nonlimiting  
15 example of a luminescent material includes luminol; nonlimiting examples of bioluminescent materials include luciferase, luciferin, and aequorin; and nonlimiting examples of suitable radioactive material include iodine ( $^{125}\text{I}$ ,  $^{131}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{111}\text{In}$  and other radioactive isotopes of indium), technetium ( $^{99}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ), thallium ( $^{201}\text{Tl}$ ), gallium ( $^{68}\text{Ga}$ ,  $^{67}\text{Ga}$ ), palladium ( $^{103}\text{Pd}$ ),  
20 molybdenum ( $^{99}\text{Mo}$ ), xenon ( $^{133}\text{Xe}$ ), fluorine ( $^{19}\text{F}$ ),  $^{153}\text{Sm}$ ,  $^{177}\text{Lu}$ , Gd, radioactive Pm, radioactive La, radioactive Yb,  $^{166}\text{Ho}$ ,  $^{90}\text{Y}$ , radioactive Sc, radioactive Re, radioactive Re,  $^{142}\text{Pr}$ ,  $^{105}\text{Rh}$ , and  $^{97}\text{Ru}$ .

In specific embodiments, the protein tyrosine kinase biomarker polypeptides of the invention are attached to macrocyclic chelators useful for conjugating  
25 radiometal ions, including, but not limited to,  $^{111}\text{In}$ ,  $^{177}\text{Lu}$ ,  $^{90}\text{Y}$ ,  $^{166}\text{Ho}$ , and  $^{153}\text{Sm}$ , to polypeptides. In a preferred embodiment, the radiometal ion associated with the macrocyclic chelators attached to the protein tyrosine kinase biomarker polypeptides of the invention is  $^{111}\text{In}$ . In another preferred embodiment, the radiometal ion associated with the macrocyclic chelator attached to the protein tyrosine kinase  
30 biomarker polypeptides of the invention is  $^{90}\text{Y}$ . In specific embodiments, the macrocyclic chelator is 1, 4, 7, 10-tetraazacyclododecane-N, N', N'', N'''-tetraacetic

acid (DOTA). In other specific embodiments, the DOTA is attached to the protein tyrosine kinase biomarker polypeptides of the invention via a linker molecule.

Examples of linker molecules useful for conjugating DOTA to a polypeptide are commonly known in the art. (See, for example, DeNardo et al., 1998, *Clin. Cancer Res.*, 4(10):2483-90; Peterson et al., 1999, *Bioconjug. Chem.*, 10(4):553-557; and Zimmerman et al., 1999, *Nucl. Med. Biol.*, 26(8):943-950, which are hereby incorporated by reference in their entirety). In addition, U.S. Patent Nos. 5,652,361 and 5,756,065, which disclose chelating agents that can be conjugated to antibodies and methods for making and using them, are hereby incorporated by reference in their  
10 entireties. Though U.S. Patent Nos. 5,652,361 and 5,756,065 focus on conjugating chelating agents to antibodies, one skilled in the art can readily adapt the methods disclosed therein in order to conjugate chelating agents to other polypeptides.

Antibodies can also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include,  
15 but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene. Techniques for conjugating therapeutic moieties to antibodies are well known, see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", In: *Monoclonal Antibodies And Cancer Therapy*, Reisfeld et al. (eds.), pp. 243-56, Alan R. Liss, Inc., 1985; Hellstrom et al., "Antibodies For Drug Delivery", In: *Controlled Drug Delivery* (2nd Ed.),  
20 Robinson et al. (eds.), pp. 623-53, Marcel Dekker, Inc., 1987; Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", In: *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera et al. (eds.), pp. 475-506, 1985; "Analysis, Results, And Future Prospective Of The Therapeutic Use Of  
25 Radiolabeled Antibody In Cancer Therapy", In: *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin et al. (eds.), pp. 303-316, Academic Press, 1985; and Thorpe et al., 1982, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.*, 62:119-158. Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate, e.g., as  
30 described in U.S. Patent No. 4,676,980 to Segal, which is incorporated herein by reference in its entirety. An antibody, i.e., an antibody specific for a protein tyrosine kinase biomarker polypeptide of this invention, with or without a therapeutic moiety

conjugated to it, and administered alone or in combination with cytotoxic factor(s) and/or cytokine(s), can be used as a therapeutic.

The antibodies of the invention can further be utilized for immunophenotyping of cell lines and biological samples. The translation product of the protein tyrosine kinase biomarker-encoding polynucleotides of the present invention can be useful as cell specific marker(s), or more specifically, as cellular marker(s) that are differentially expressed at various stages of differentiation and/or maturation of particular cell types. Monoclonal antibodies directed against a specific epitope, or combination of epitopes, allow for the screening of cellular populations expressing the marker. Various techniques utilizing monoclonal antibodies can be employed to screen for cellular populations expressing the marker(s), including magnetic separation using antibody-coated magnetic beads, "panning" with antibody(ies) attached to a solid matrix (i.e., tissue culture plate), and flow cytometry (See, e.g., U.S. Patent No. 5,985,660; Morrison et al., 1999, *Cell*, 96:737-749; and L.J. Wysocki and V.L. Sato, 1978, *Proc. Natl. Acad. Sci. USA*, 75(6):2844-8).

These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i. e. minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

Antibodies according to this invention can be assayed for immunospecific binding by any method known in the art. The immunoassays which can be used include, but are not limited to, competitive and non-competitive assay systems using techniques such as BIAcore analysis, FACS (Fluorescence Activated Cell Sorter) analysis, immunofluorescence, immunocytochemistry, Western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assays), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few. Such assays are routine and well known and practiced in the art (see, e.g., Ausubel et al, eds, 1994, *Current Protocols in*

*Molecular Biology*, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Nonlimiting, exemplary immunoassays are described briefly below.

Immunoprecipitation protocols generally comprise lysing a population of cells  
5 in a lysis buffer such as RIPA buffer (i.e., 1% NP-40 or Triton X-100, 1% sodium  
deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1%  
Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e.g.,  
EDTA, PMSF, aprotinin, sodium vanadate); adding the antibody of interest to the cell  
lysate; incubating for a period of time (e.g., 1 to 4 hours) at 4°C; adding protein A  
10 and/or protein G sepharose beads to the cell lysate; incubating for about 60 minutes or  
more at 4°C; washing the beads in lysis buffer; and resuspending the beads in  
SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a  
particular antigen can be assessed by, for example, Western blot analysis. One of skill  
in the art would be knowledgeable as to the parameters that can be modified to  
15 increase the binding of the antibody to an antigen and decrease the background (e.g.,  
pre-clearing the cell lysate with sepharose beads). For further discussion regarding  
immunoprecipitation protocols, see, e.g., Ausubel et al, eds, 1994, *Current Protocols*  
*in Molecular Biology*, Vol. 1, John Wiley & Sons, Inc., New York, at 10.16.1.

Western blot analysis generally comprises preparing protein samples;  
20 electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%-20% SDS  
PAGE depending on the molecular weight of the antigen); transferring the protein  
sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or  
nylon; blocking the membrane in blocking solution (e. g., PBS with 3% BSA or  
nonfat milk); washing the membrane in washing buffer (e.g., PBS-Tween 20);  
25 blocking the membrane with primary antibody (the antibody of interest) diluted in  
blocking buffer; washing the membrane in washing buffer; blocking the membrane  
with a secondary antibody (which recognizes the primary antibody, e.g., an anti-  
human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or  
alkaline phosphatase) or radioactive molecule (e.g., <sup>32</sup>P or <sup>125</sup>I) diluted in blocking  
30 buffer; washing the membrane in wash buffer; and detecting the presence of the  
bound antigen. One of skill in the art would be knowledgeable as to the parameters  
that can be modified to increase the signal detected and to reduce the background

noise. For further discussion regarding Western blot protocols, see, e.g., Ausubel et al, eds, 1994, *Current Protocols in Molecular Biology*, Vol. 1, John Wiley & Sons, Inc., New York, at 10.8.1.

ELISAs comprise preparing antigen; coating the wells of a 96 well microtiter plate with antigen; adding to the wells the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase); incubating for a period of time; and detecting the presence of the antigen. In ELISAs, the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest bound to antigen) conjugated to a detectable compound can be added to the wells. Further, instead of coating the wells with antigen, the antibodies can be first coated onto the well. In this case, a second antibody conjugated to a detectable compound can be added to the antibody-coated wells following the addition of the antigen of interest. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected, as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs, see, e.g., Ausubel et al, eds, 1994, *Current Protocols in Molecular Biology*, Vol. 1, John Wiley & Sons, Inc., New York, at 11.2.1.

The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay involving the incubation of labeled antigen (e.g.,  $^3\text{H}$  or  $^{125}\text{I}$ ), or a fragment or variant thereof, with the antibody of interest in the presence of increasing amounts of labeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a protein tyrosine kinase biomarker and the binding off rates can be determined from the data by Scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the tyrosine kinase biomarker protein is incubated with an antibody of interest conjugated to a labeled compound (e.g., a compound labeled with  $^3\text{H}$  or  $^{125}\text{I}$ ) in the presence of increasing amounts of an unlabeled second antibody. This kind of competitive assay between two antibodies can also be used to determine if two antibodies bind to the same or different epitopes on an antigen.

In a preferred embodiment, BIAcore kinetic analysis is used to determine the binding on and off rates of antibodies (including antibody fragments or variants thereof) to a tyrosine kinase biomarker protein, or fragments of a tyrosine kinase biomarker protein. Kinetic analysis comprises analyzing the binding and dissociation  
5 of antibodies from chips with immobilized tyrosine kinase biomarker protein on the chip surface.

It is to be further understood that the above-described techniques for the production, expression, isolation, and manipulation of antibody molecules, for example, by recombinant techniques involving molecular biology, as well as by other  
10 techniques related to the analysis of polynucleotides and proteins, are applicable to other polypeptide or peptide molecules of the invention as described herein, in particular, the tyrosine kinase biomarker polypeptides or peptides themselves, as applicable or warranted. in accordance with the various embodiments of this invention.

15 The present invention also embraces a kit for determining, predicting, or prognosing drug susceptibility or resistance by a patient having a disease, particularly a cancer or tumor, preferably, a breast cancer or tumor. Such kits are useful in a clinical setting for use in testing patient's biopsied tumor or cancer samples, for example, to determine or predict if the patient's tumor or cancer will be resistant or  
20 sensitive to a given treatment or therapy with a drug, compound, chemotherapy agent, or biological treatment agent. Provided in the kit are the predictor set comprising those polynucleotides correlating with resistance and sensitivity to protein tyrosine kinase modulators in a particular biological system, particularly protein tyrosine kinase inhibitors, and preferably comprising a microarray; and, in suitable containers,  
25 the modulator compounds for use in testing cells from patient tissue or patient samples for resistance/sensitivity; and instructions for use. Such kits encompass predictor set comprising those polynucleotides correlating with resistance and sensitivity to modulators of protein tyrosine kinases including members of the Src family of tyrosine kinases, for example, Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as  
30 well as other protein tyrosine kinases, including, Bcr-abl, Jak, PDGFR, c-kit and Eph receptors,



Also, as explained above, the kit is not limited to microarrays, but can encompass a variety of methods and systems by which the expression of the predictor/marker polynucleotides can be assayed and/or monitored, both at the level of mRNA and of protein, for example, via PCR assays, e.g., RT-PCR and immunoassay, such as ELISA. In kits for performing PCR, or *in situ* hybridization, for example, nucleic acid primers or probes from the sequences of one or more of the predictor polynucleotides, such as those described herein, in addition to buffers and reagents as necessary for performing the method, and instructions for use. In kits for performing immunoassays, e.g. ELISAs, immunoblotting assays, and the like, antibodies, or bindable portions thereof, to the protein tyrosine kinase biomarker polypeptides of the invention, or to antigenic or immunogenic peptides thereof, are supplied, in addition to buffers and reagents as necessary for performing the method, and instructions for use. The kits according to the present invention can also comprise predictor polynucleotides as set forth in Table 2, and/or one or more of the specific predictor polynucleotide subsets as presented in Tables 4-5 herein.

In another embodiment, the present invention embraces the use of one or more polynucleotides among those of the predictor polynucleotides identified herein that can serve as targets for the development of drug therapies for disease treatment. Such targets may be particularly applicable to treatment of breast diseases, such as breast cancers or tumors. Indeed, because these predictor polynucleotides are differently expressed in sensitive and resistant cells, their expression pattern is correlated with relative intrinsic sensitivity of cells to treatment with compounds that interact with and inhibit protein tyrosine kinases. Accordingly, the polynucleotides highly expressed in resistant cells can serve as targets for the development of drug therapies for the tumors which are resistant to protein tyrosine kinase inhibitor compounds, for example, Src tyrosine kinase inhibitors.

In another embodiment, the present invention embraces antisense and/or siRNAi reagents as specific modulators of the predictor polynucleotides of the present invention. In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in one or more of the sequences provided as SEQ ID NO:1 thru 137, or the complementary strand thereof. In one embodiment, antisense sequence is generated internally by the organism, in

another embodiment, the antisense sequence is separately administered (see, for example, O'Connor, *Neurochem.*, 56:560 (1991). *Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression*, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA, or  
5 through triple-helix formation. Antisense techniques are discussed for example, in Okano, *Neurochem.*, 56:560 (1991); *Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression*, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., *Nucleic Acids Research*, 6:3073 (1979); Cooney et al., *Science*, 241:456 (1988); and Dervan et al., *Science*, 251:1300 (1991). The  
10 methods are based on binding of a polynucleotide to a complementary DNA or RNA.

For example, the use of c-myc and c-myb antisense RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described. (Wickstrom et al. (1988); Anfossi et al. (1989)). These experiments were performed in vitro by incubating cells with the oligoribonucleotide.  
15 A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given antisense RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked by an EcoRI site on the 5' end and a HindIII site on the 3' end. Next, the pair of oligonucleotides is heated at 90°C for one minute and then annealed in 2X ligation buffer (20mM TRIS  
20 HCl pH 7.5, 10mM MgCl<sub>2</sub>, 10mM dithiothreitol (DTT) and 0.2 mM ATP) and then ligated to the EcoRI/Hind III site of the retroviral vector PMV7 (WO 91/15580).

For example, the 5' coding portion of a polynucleotide that encodes the mature polypeptide of the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is  
25 designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The antisense RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide. Antisense oligonucleotides may be single or double stranded. Double stranded RNA's may be designed based upon the  
30 teachings of Paddison et al., *Proc. Nat. Acad. Sci.*, 99:1443-1448 (2002); and International Publication Nos. WO 01/29058, and WO 99/32619; which are hereby incorporated herein by reference.

In one embodiment, the antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the antisense nucleic acid of the invention. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding a polypeptide of the invention, or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, *Nature*, 29:304-310 (1981)), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., *Cell*, 22:787-797 (1980)), the herpes thymidine promoter (Wagner et al., *Proc. Natl. Acad. Sci. U.S.A.*, 78:1441-1445 (1981)), the regulatory sequences of the metallothionein gene (Brinster et al., *Nature*, 296:39-42 (1982)), etc.

The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a gene of interest. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA" referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded antisense nucleic acids of the invention, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA sequence of the invention it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

Oligonucleotides that are complementary to the 5' end of the message, e.g., the 5' untranslated sequence up to and including the AUG initiation codon, should work

most efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., *Nature*, 372:333-335 (1994). Thus, oligonucleotides complementary to either the 5' - or 3' - non- translated, non-coding regions of a polynucleotide sequence of the invention could be used in an antisense approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5' -, 3' - or coding region of mRNA, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

The polynucleotides of the invention can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors in vivo), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., *Proc. Natl. Acad. Sci. U.S.A.* 86:6553-6556 (1989); Lemaitre et al., *Proc. Natl. Acad. Sci.*, 84:648-652 (1987); PCT Publication NO: WO88/09810, published December 15, 1988) or the blood-brain barrier (see, e.g., PCT Publication NO: WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents. (See, e.g., Krol et al., *BioTechniques*, 6:958-976 (1988)) or intercalating agents. (See, e.g., Zon, *Pharm. Res.*, 5:539-549 (1988)). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

Double stranded RNA's may be designed based upon the teachings of Paddison et al., *Proc. Nat. Acad. Sci.*, 99:1443-1448 (2002); and International

Publication Nos. WO 01/29058, and WO 99/32619; which are hereby incorporated herein by reference.

SiRNA reagents are specifically contemplated by the present invention. Such reagents are useful for inhibiting expression of the polynucleotides of the present invention and may have therapeutic efficacy. Several methods are known in the art for the therapeutic treatment of disorders by the administration of siRNA reagents. One such method is described by Tiscornia et al (PNAS, 100(4):1844-1848 (2003)), which is incorporated by reference herein in its entirety.

The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded

hybrids with complementary RNA in which, contrary to the usual b-units, the strands run parallel to each other (Gautier et al., Nucl. Acids Res., 15:6625-6641 (1987)). The oligonucleotide is a 2-O-methylribonucleotide (Inoue et al., Nucl. Acids Res., 15:6131-6148 (1987)), or a chimeric RNA-DNA analogue (Inoue et al., FEBS Lett. 5 215:327-330 (1987)).

Polynucleotides of the invention may be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein et al. 10 (Nucl. Acids Res., 16:3209 (1988)), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., Proc. Natl. Acad. Sci. U.S.A., 85:7448-7451 (1988)), etc.

While antisense nucleotides complementary to the coding region sequence of the invention could be used, those complementary to the transcribed untranslated 15 region are most preferred.

Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al, Science, 247:1222-1225 (1990). While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy mRNAs 20 corresponding to the polynucleotides of the invention, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known 25 in the art and is described more fully in Haseloff and Gerlach, Nature, 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within each nucleotide sequence disclosed in the sequence listing. Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the mRNA corresponding to the polynucleotides of the invention; i.e., to increase 30 efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

As in the antisense approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express the polynucleotides of the invention in vivo. DNA constructs encoding the ribozyme may be introduced into the cell in the same manner as described above for the introduction of antisense encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous messages and inhibit translation. Since ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

Antagonist/agonist compounds may be employed to inhibit the cell growth and proliferation effects of the polypeptides of the present invention on neoplastic cells and tissues, i.e. stimulation of angiogenesis of tumors, and, therefore, retard or prevent abnormal cellular growth and proliferation, for example, in tumor formation or growth.

The antagonist/agonist may also be employed to prevent hyper-vascular diseases, and prevent the proliferation of epithelial lens cells after extracapsular cataract surgery. Prevention of the mitogenic activity of the polypeptides of the present invention may also be desirable in cases such as restenosis after balloon angioplasty.

The antagonist/agonist may also be employed to prevent the growth of scar tissue during wound healing.

The antagonist/agonist may also be employed to treat, prevent, and/or diagnose the diseases described herein.

Thus, the invention provides a method of treating or preventing diseases, disorders, and/or conditions, including but not limited to the diseases, disorders, and/or conditions listed throughout this application, associated with overexpression of a polynucleotide of the present invention by administering to a patient (a) an antisense molecule directed to the polynucleotide of the present invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention.

## EXAMPLES

The Examples herein are meant to exemplify the various aspects of carrying out the invention and are not intended to limit the scope of the invention in any way. The Examples do not include detailed descriptions for conventional methods employed, such as in the construction of vectors, the insertion of cDNA into such vectors, or the introduction of the resulting vectors into the appropriate host. Such methods are well known to those skilled in the art and are described in numerous publications, for example, Sambrook, Fritsch, and Maniatis, Molecular Cloning: A Laboratory Manual, 2<sup>nd</sup> Edition, Cold Spring Harbor Laboratory Press, USA, (1989).

10

## EXAMPLE 1 – METHODS

IC<sub>50</sub> determination--*in vitro* cytotoxicity assay

The protein tyrosine kinase inhibitor compound (described in international application WO 00/62778, published October 26, 2000) was tested for cytotoxicity *in vitro* against a panel of twenty-three human breast cell lines available from the American Type Culture Collection, ATCC, except H3396, which was obtained from Pacific Northwest Research Institute, Seattle WA. The MCF7/Her2 cell line was established by stable transfection of MCF7 cells with the HER2 gene. Cytotoxicity was assessed in cells by the MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxy-methoxyphenyl)-2-(4-sulphenyl)-2H-tetrazolium, inner salt) assay (T.L. Riss et al., 1992, *Mol. Biol. Cell*, 3 (Suppl.):184a).

To carry out the assays, the breast cells were plated at 4,000 cells/well in 96 well microtiter plates, and 24 hours later, serially diluted drugs were added. The concentration range for the protein tyrosine kinase inhibitor compound BMS-A used in the cytotoxicity assay was from 5 µg/ml to 0.0016 µg/ml (roughly 10 µM to 0.0032 µM).

The cells were incubated at 37°C for 72 hours at which time the tetrazolium dye, MTS (333 µg/ml final concentration), in combination with the electron coupling agent phenazine methosulfate (25 µM final concentration), was added. A dehydrogenase enzyme in live cells reduces the MTS to a form that absorbs light and can be quantified spectrophotometrically at 492 nM. The greater the absorbency the





than 39,000 transcripts derived from approximately 33,000 well-substantiated human polynucleotides.

#### Preprocessing of microarray data

Scanned image files were visually inspected for artifacts and analyzed with  
5 GeneChip® Expression Analysis software MAS 5.0 (Affymetrix, Santa Clara, CA).  
The "Detection Call" (Affymetrix Genechip® Expression Analysis Technical Manual,  
2001) is used to determine whether a transcript is detected within one sample; the  
"Signal" (Affymetrix Genechip® Expression Analysis Technical Manual, 2001)  
measures the relative abundance of a transcript. The trimmed mean intensity for each  
10 chip was scaled to 1,500 (see, Affymetrix Genechip® Expression Analysis Technical  
Manual, 2001) in order to account for any minor differences in global chip intensity,  
so that the overall expression level for each cell line was comparable. Affymetrix  
control sequences were removed prior to analysis.

Of a total of 44,792 probe sets on the HG-U133 arrays, 15,707 represented  
15 probe sets were not detected (Absent Call; p-value >0.06) across all of the 23 breast  
cell lines using the Affymetrix GeneChip® Expression Analysis algorithm; these  
undetected polynucleotides were excluded from further analysis.

The remaining data containing 29,085 probe sets were transferred to the  
GeneCluster software (Whitehead Institute; T.R. Golub et al., 1999, *Science*, 286:531-  
20 537). A threshold filter was applied to the polynucleotide expression values of the  
remaining data to remove low and high polynucleotide expression values that were  
not likely to be in the linear range of the Affymetrix fluorescent scanner. The  
threshold filter converted all polynucleotide expression values that were below 100  
units to 100 units, and all polynucleotide expression values that were above 45,000  
25 units to 45,000 units. All represented polynucleotides whose polynucleotide  
expression values were between 100 and 45,000 were not changed.

A second "variation filter" was then applied to the data set to find  
polynucleotides that were likely to correlate with different properties and features of  
the 23 cell lines. The object of the second filter was to select those polynucleotides  
30 whose expression pattern varied across the data set, because a polynucleotide that  
does not vary can not provide information about differing properties of the 23 cell line

panel. For example, if there are two populations of cells within the data set, e.g., fast growing cells and slow growing cells, then a polynucleotide whose expression is constant, or whose expression does not change substantially, can not yield information that would correlate to fast or slow cell growth.

5           The second variation filter was formulated to determine the expression pattern of each polynucleotide across the 23 breast cell lines and to find polynucleotides that passed the following criteria:

1. The polynucleotide must show a three-fold change in absolute expression, i.e., as depicted in the formula:

10

$$\frac{\text{expression value in any given cell line}}{\text{expression value in any other cell line}} > 3 \text{ or } < 0.33$$

15           2. In addition to 1, the three-fold change must represent an absolute difference of 1000 expression units.

          3. In addition, the criteria in #1 and #2 above must be met on four independent occasions within the data set, i.e., Cell line A/B, Cell line E/F, Cell line C/U and Cell line T/G. (The algorithm does not use a single expression value for one cell line on multiple occasions, i.e., Cell Line A/B, Cell line A/G, Cell line A/F and  
20   Cell line B/F).

          The second variation filter reduced the data set to 5322 polynucleotides. After the second variation filter, the expression value for each polynucleotide was log transformed and normalized to the mean across all of the 23 samples (mean set to 0 and standard deviation set to 1). This normalized data set was used to select  
25   polynucleotides which significantly correlated with the property of sensitivity toward a drug class as described herein.

#### Drug (BMS-A) treatment of breast cell lines and selection of polynucleotides modified by the drug

          The 11 breast cell lines (indicated in bold in the Table 1) with an IC<sub>50</sub> ranging  
30   from 0.0055 to 9.5 µM were used in a drug induction study employing the BMS-A protein tyrosine kinase inhibitor. Cells were seeded in a 10 cm<sup>2</sup> culture plate in cell culture medium as described herein and were cultured for 24 hours at 37°C. The

medium was then changed to medium containing drug (0.4  $\mu$ M BMS-A compound in 0.1% DMSO, Sigma); the cells were incubated for another 24 hours, and then lysed for RNA isolation. The expression profiling was performed as described above and data were analyzed using GeneChip<sup>®</sup> Expression Analysis software MAS 5.0 (Affymetrix, Santa Clara, CA). The expression data of a drug treated cell line were compared pair-wise to data from the same cell line untreated with drug. A change in p-value was calculated, indicating an increase, decrease or no change in polynucleotide expression. When the p-value was less than 0.0025, the change was considered to be significant. This analysis was performed for all 11 cell lines to compare the polynucleotide expression with or without drug treatment.

## EXAMPLE 2 – PCR EXPRESSION PROFILING

RNA quantification is performed using the Taqman<sup>®</sup> real-time-PCR fluorogenic assay. The Taqman<sup>®</sup> assay is one of the most precise methods for assaying the concentration of nucleic acid templates.

RNA is prepared using standard methods, preferably, employing the RNeasy Maxi Kit commercially available from Qiagen (Valencia, CA). A cDNA template for real-time PCR can be generated using the Superscript<sup>™</sup> First Strand Synthesis system for RT-PCR. Representative forward and reverse RT-PCT primers for each of the protein tyrosine kinase biomarker polynucleotides of the present invention are provided in Table 6.

SYBR Green real-time PCR reactions are prepared as follows: The reaction mix contains 20 ng first strand cDNA; 50 nM Forward Primer; 50 nM Reverse Primer; 0.75X SYBR Green I (Sigma); 1X SYBR Green PCR Buffer (50 mM Tris-HCl pH 8.3, 75 mM KCl); 10% DMSO; 3 mM MgCl<sub>2</sub>; 300  $\mu$ M each dATP, dGTP, dTTP, dCTP; 1 U Platinum<sup>®</sup> Taq DNA Polymerase High Fidelity (Cat# 11304-029; Life Technologies; Rockville, MD). Real-time PCR is performed using an Applied Biosystems 5700 Sequence Detection System. Conditions are 95°C for 10 minutes (denaturation and activation of Platinum<sup>®</sup> Taq DNA Polymerase), 40 cycles of PCR (95°C for 15 seconds, 60°C for 1 minute). PCR products are analyzed for uniform melting using an analysis algorithm built into the 5700 Sequence Detection System.

cDNA quantification used in the normalization of template quantity is performed using Taqman® technology. Taqman® reactions are prepared as follows: The reaction mix comprises 20 ng first strand cDNA; 25 nM GAPDH-F3, Forward Primer; 250 nM GAPDH-R1 Reverse Primer; 200 nM GAPDH-PVIC Taqman®  
 5 Probe (fluorescent dye labeled oligonucleotide primer); 1X Buffer A (Applied Biosystems); 5.5 mM MgCl<sub>2</sub>; 300 μM dATP, dGTP, dTTP, dCTP; and 1 U Amplitaq Gold (Applied Biosystems). GAPDH (D-glyceraldehyde-3-phosphate dehydrogenase) is used as a control to normalize mRNA levels. Real-time Taqman® PCR is performed using an Applied Biosystems 7700 Sequence Detection System.  
 10 Conditions are 95°C for 10 minutes (denaturation and activation of Amplitaq Gold), 40 cycles of PCR (95°C for 15 seconds, 60°C for 1 minute).

The sequences for the GAPDH oligonucleotides used in the Taqman® reactions are as follows:

- 15 GAPDH-F3: 5'-AGCCGAGCCACATCGCT-3' (SEQ ID NO:531);  
 GAPDH-R1: 5'-GTGACCAGGCGCCCAATAC-3' (SEQ ID NO:532); and  
 GAPDH-PVIC Taqman® Probe -VIC-5'-  
 CAAATCCGTTGACTCCGACCTTCACCTT-3' TAMRA (SEQ ID NO:533).

20 The Sequence Detection System generates a Ct (threshold cycle) value that is used to calculate a concentration for each input cDNA template. cDNA levels for each polynucleotide of interest are normalized to GAPDH cDNA levels to compensate for variations in total cDNA quantity in the input sample. This is done by generating GAPDH Ct values for each cell line. Ct values for the polynucleotide of  
 25 interest and GAPDH are inserted into a modified version of the  $\delta\delta Ct$  equation (Applied Biosystems Prism® 7700 Sequence Detection System User Bulletin #2), which is used to calculate a GAPDH normalized relative cDNA level for each specific cDNA. The  $\delta\delta Ct$  equation is as follows: relative quantity of nucleic acid template  $= 2^{\delta\delta Ct} = 2^{(\delta Ct_a - \delta Ct_b)}$ , where  $\delta Ct_a = Ct_{\text{target}} - Ct_{\text{GAPDH}}$ , and  $\delta Ct_b = Ct_{\text{reference}} - Ct_{\text{GAPDH}}$ . (No reference cell line is used for the calculation of relative quantity;  $\delta Ct_b$   
 30 is defined as 21).

### EXAMPLE 3 – PRODUCTION OF AN ANTIBODY DIRECTED AGAINST PROTEIN TYROSINE KINASE BIOMARKER POLYPEPTIDES

Anti-protein tyrosine kinase biomarker polypeptide antibodies of the present  
5 invention can be prepared by a variety of methods as detailed hereinabove. As one  
example of an antibody-production method, cells expressing a polypeptide of the  
present invention are administered to an animal as immunogen to induce the  
production of sera containing polyclonal antibodies directed against the expressed  
polypeptide. In a preferred method, the expressed polypeptide is prepared, preferably  
10 isolated and/or purified, to render it substantially free of natural contaminants using  
techniques commonly practiced in the art. Such a preparation is then introduced into  
an animal in order to produce polyclonal antisera of greater specific activity for the  
expressed and isolated polypeptide.

In a most preferred method, the antibodies of the present invention are  
15 monoclonal antibodies (or protein binding fragments thereof) and can be prepared  
using hybridoma technology as detailed hereinabove. Cells expressing the  
polypeptide can be cultured in any suitable tissue culture medium; however, it is  
frequently preferable to culture cells in Earle's modified Eagle's medium  
supplemented to contain 10% fetal bovine serum (inactivated at about 56°C), and  
20 supplemented to contain about 10 g/l nonessential amino acids, about 1.0 U/ml  
penicillin, and about 100 µg/ml streptomycin.

The splenocytes of immunized (and boosted) mice are extracted and fused  
with a suitable myeloma cell line. Any suitable myeloma cell line can be employed in  
accordance with the present invention; however, it is preferable to employ the parent  
25 myeloma cell line SP2/0, available from the ATCC. After fusion, the resulting  
hybridoma cells are selectively maintained in HAT medium, and then cloned by  
limiting dilution as described, for example, by Wands et al. (1981, *Gastroenterology*,  
80:225-232). The hybridoma cells obtained through such a selection process are then  
assayed to identify those cell clones that secrete antibodies capable of binding to the  
30 polypeptide immunogen, or a portion thereof.

Alternatively, additional antibodies capable of binding to the polypeptide can  
be produced in a two-step procedure using anti-idiotypic antibodies. Such a method

makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain a second antibody that binds to a first antibody. In accordance with this method, protein-specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an immunized animal are then used to produce  
5 hybridoma cells, and the hybridoma cells are screened to identify clones that produce an antibody whose ability to bind to the protein-specific antibodies can be blocked by the protein. Such antibodies comprise anti-idiotypic antibodies to the protein-specific antibody and can be used to immunize an animal to induce the formation of further protein-specific antibodies.

10 For *in vivo* use of antibodies in humans, it may be preferable to use "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric antibodies are known and practiced in the art. (See, e.g., for review, Morrison, 1985, *Science*, 229:1202); Oi et al., 1986,  
15 *BioTechniques*, 4:214; Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., 1984, *Nature*, 312:643; and Neuberger et al., 1985, *Nature*, 314:268).

#### 20 EXAMPLE 4 – IMMUNOFLUORESCENCE ASSAYS

The following immunofluorescence protocol can be used, for example, to verify protein tyrosine kinase biomarker expression in cells, or, for example, to check for the presence of one or more antibodies that bind protein tyrosine kinase biomarkers (polypeptides or peptides) expressed on the surfaces of cells. Briefly,  
25 Lab-Tek II chamber slides are coated overnight at 4°C with 10 µg/ml of bovine collagen Type II in DPBS containing calcium and magnesium (DPBS++). The slides are then washed twice with cold DPBS++ and seeded with approximately 8000 CHO cells transfected with a vector comprising the coding sequence for a protein tyrosine kinase biomarker of the present invention or with CHO cells transfected with vector  
30 alone (control) in a total volume of 125 µl and incubated at 37°C in the presence of 95% oxygen / 5% carbon dioxide.

Thereafter, the culture medium is gently removed by aspiration and the adherent cells are washed twice with DPBS++ at ambient temperature. The slides are blocked with DPBS++ containing 0.2% BSA (blocker) at 0-4°C for one hour. The blocking solution is gently removed by aspiration, and 125 µl of antibody containing solution (an antibody containing solution may be, for example, a hybridoma culture supernatant which is usually used undiluted, or serum/plasma which is usually diluted, e.g., a dilution of about 1:50, 1:100, 1:1000, and the like). The slides are incubated for 1 hour at 0-4°C. Antibody solutions are then gently removed by aspiration and the cells are washed 5 times with 400 µl of ice cold blocking solution. Next, 125 µl of 1 µg/ml rhodamine labeled secondary antibody (e.g., anti-human IgG) in blocker solution is added to the cells. Again, cells are incubated for 1 hour at 0-4°C.

The secondary antibody solution is then gently removed by aspiration and the cells are washed 3 times with 400 µl of ice cold blocking solution, and 5 times with cold DPBS++. The cells are then fixed with 125 µl of 3.7% formaldehyde in DPBS++ for 15 minutes at ambient temperature. Thereafter, the cells are washed 5 times with 400 µl of DPBS++ at ambient temperature. Finally, the cells are mounted in 50% aqueous glycerol and viewed using a fluorescence microscope using rhodamine filters.

## EXAMPLE 5 – COMPLIMENTARY SEQUENCES.

Antisense molecules or nucleic acid sequences complementary to the protein tyrosine kinase biomarker polypeptides-encoding sequence, or any part thereof, is used to decrease or to inhibit the expression of naturally occurring protein tyrosine kinase biomarker polypeptides. Although the use of antisense or complementary oligonucleotides comprising about 15 to 35 base-pairs is described, essentially the same procedure is used with smaller or larger nucleic acid sequence fragments. An oligonucleotide based on the coding sequence of protein tyrosine kinase biomarker polypeptides, as depicted in SEQ ID NO:1 thru 137, for example, is used to inhibit expression of naturally occurring protein tyrosine kinase biomarker polypeptides. The complementary oligonucleotide is typically designed from the most unique 5' sequence and is used either to inhibit transcription by preventing promoter binding to



the coding sequence, or to inhibit translation by preventing the ribosome from binding to the protein tyrosine kinase biomarker polypeptides-encoding transcript, among others. However, other regions may also be targeted.

Using an appropriate portion of the signal and 5' sequence of SEQ ID NO:1 thru 137, an effective antisense oligonucleotide includes any of about 15-35 nucleotides spanning the region which translates into the signal or 5' coding sequence, among other regions, of the polypeptide as depicted in SEQ ID NO:138 thru 256. Appropriate oligonucleotides may be designed using OLIGO 4.06 software and the protein tyrosine kinase biomarker polypeptides coding sequence (SEQ ID NO:1 thru 137). Preferred oligonucleotides are deoxynucleotide, or chimeric deoxynucleotide/ribonucleotide based and are provided below. The oligonucleotides may be synthesized using chemistry essentially as described in U.S. Patent No. 5,849,902; which is hereby incorporated herein by reference in its entirety.

Representative RNAi reagent sequences are as follows:

Target Name	Sense Strand RNAi Reagent	SEQ ID NO:	Anti-Sense Strand RNAi Reagent	SEQ ID NO:
caveolin 1-1	CAGGGCAACAUCUACAA GCTT	534	GCUUGUAGAUGUUGCCCU GTT	546
caveolin 1-2	GCAAGUGUACGACGCGC ACTT	535	GUGCGGUCGUACACUUG CTT	547
caveolin 1-3	CCGCUUGCUGUCUGCCCU CTT	536	GAGGGCAGACAGCAAGCG GTT	548
caveolin 1-4	CAUCUGGGCAGUUGUAC CATT	537	UGGUACAACUGCCCAGAU GTT	549
caveolin 2-1	CUACGCACUCCUUUGACA ATT	538	UUGUCAAGGAGUGCGUA GTT	550
caveolin 2-2	AGUGUGGAUCUGCAGCC AUTT	539	AUGGCUGCAGAUCCACAC UTT	551
caveolin 2-3	GUUCCUGACGGUGUUCC UGTT	540	CAGGAACACCGUCAGGAA CTT	552
caveolin 2-4	UUGCGGGAUUCUCUUU GCTT	541	GCAAAGAGAAUUCCCGCA ATT	553
ephA2-1	GGAAGUGGUACUGCUGG ACTT	542	GUCCAGCAGUACCACUUC CTT	554
ephA2-2	CUUCCAGAAGCGCCUGU UCTT	543	GAACAGGCGCUUCUGGAA GTT	555
ephA2-3	GAGCCCCGUAUGCACUG UGTT	544	CACAGUGCAUACGGGGCU CTT	556
ephA2-4	CUACACCUUCACCGUGGA GTT	545	CUCCACGGUGAAGGUGUA GTT	557

15

Transfection of post-quiescent A549 cells With AntiSense Oligonucleotides.

Materials needed:

- A549 cells can be maintained in DMEM with high glucose (Gibco-BRL) supplemented with 10% Fetal Bovine Serum, 2mM L-Glutamine, and 1X penicillin/streptomycin.
- Opti-MEM (Gibco-BRL)
- Lipofectamine 2000 (Invitrogen)
- Antisense oligomers (Qiagen)
- Polystyrene tubes.
- Tissue culture treated plates.

Quiescent cells are prepared as follows:

- Day 0: 300, 000 A549 cells are seeded in a T75 tissue culture flask in 10 ml of A549 media (as specified above), and incubated in at 37°C, 5% CO<sub>2</sub> in a humidified incubator for 48 hours.
- Day 2: The T75 flasks are rocked to remove any loosely adherent cells, and the A549 growth media removed and replenished with 10 ml of fresh A549 media. The cells are cultured for six days without changing the media to create a quiescent cell population.
- Day 8: Quiescent cells are plated in multi-well format and transfected with antisense oligonucleotides.

A549 cells are transfected according to the following:

1. Trypsinize T75 flask containing quiescent population of A549 cells.
2. Count the cells and seed 24-well plates with 60K quiescent A549 cells per well.
3. Allow the cells to adhere to the tissue culture plate (approximately 4 hours).
4. Transfect the cells with antisense and control oligonucleotides according to the following:

- a. A 10X stock of lipofectamine 2000 (10 ug/ml is 10X) may be prepared, and diluted lipid is allowed to stand at RT for 15 minutes.  
Stock solution of lipofectamine 2000 is 1 mg/ml.  
10 X solution for transfection is 10 ug/ml.  
5 To prepare 10X solution, dilute 10 ul of lipofectamine 2000 stock per 1 ml of Opti-MEM (serum free media).
- b. A 10X stock of each oligomer may be prepared for use in the transfection.  
Stock solutions of oligomers are at 100 uM in 20 mM HEPES, pH 7.5.  
10 10X concentration of oligomer may be 0.25 uM.  
To prepare the 10X solutions, dilute 2.5 ul of oligomer per 1 ml of Opti-MEM.
- c. Equal volumes of the 10X lipofectamine 2000 stock and the 10X oligomer solutions are mixed well, and incubated for 15 minutes at RT  
15 to allow complexation of the oligomer and lipid. The resulting mixture is 5X.
- d. After the 15 minute complexation, 4 volumes of full growth media is added to the oligomer/lipid complexes (solution may be 1X).
- e. The media may be aspirated from the cells, and 0.5 ml of the 1X oligomer/lipid complexes added to each well.  
20
- f. The cells are incubated for 16-24 hours at 37°C in a humidified CO<sub>2</sub> incubator.
- g. Cell pellets are harvested for RNA isolation and TaqMan analysis of the expression of the protein tyrosine kinase biomarker polypeptides to  
25 assess level of knock-down.

### TaqMan Reactions

- Quantitative RT-PCR analysis may be performed on total RNA preps that are treated with DNaseI or poly A selected RNA. The Dnase treatment may be performed  
30 using methods known in the art, though preferably using a Qiagen RNeasy kit to purify the RNA samples, wherein DNase I treatment is performed on the column.

Briefly, a master mix of reagents may be prepared according to the following table:

#### Dnase I Treatment

<u>Reagent</u>	<u>Per r'xn (in uL)</u>
10x Buffer	2.5
Dnase I (1 unit/ul @ 1 unit per ug sample)	2
DEPC H <sub>2</sub> O	0.5
RNA sample @ 0.1 ug/ul	20
(2-3 ug total)	
Total	25

5

Next, 5 ul of master mix may be aliquoted per well of a 96-well PCR reaction plate (PE part # N801-0560). RNA samples are adjusted to 0.1 ug/ul with DEPC treated H<sub>2</sub>O (if necessary), and 20 ul may be added to the aliquoted master mix for a final reaction volume of 25 ul.

10 The wells are capped using strip well caps (PE part # N801-0935), placed in a plate, and briefly spun in a plate centrifuge (Beckman) to collect all volume in the bottom of the tubes. Generally, a short spin up to 500rpm in a Sorvall RT is sufficient

The plates are incubated at 37°C for 30 mins. Then, an equal volume of 0.1mM EDTA in 10mM Tris may be added to each well, and heat inactivated at 70°C

15 for 5 min. The plates are stored at -80°C upon completion.

#### RT reaction

A master mix of reagents may be prepared according to the following table:

20

#### RT Reaction

<u>Reagent</u>	<u>RT</u> <u>Per Rx'n (in ul)</u>	<u>No RT</u> <u>Per Rx'n (in ul)</u>
10x RT buffer	5	2.5
MgCl <sub>2</sub>	11	5.5
DNTP mixture	10	5
Random Hexamers	2.5	1.25
Rnase inhibitors	1.25	0.625

<u>Reagent</u>	<u>RT</u> <u>Per Rx'n (in ul)</u>	<u>No RT</u> <u>Per Rx'n (in ul)</u>
RT enzyme	1.25	-
Total RNA 500ng (100ng no RT )	19.0 max	10.125 max
DEPC H <sub>2</sub> O	-	-
Total	50uL	25uL

Samples are adjusted to a concentration so that 500ng of RNA is added to each RT rx'n (100ng for the no RT). A maximum of 19 ul can be added to the RT rx'n mixture (10.125 ul for the no RT.) Any remaining volume up to the maximum values  
 5 may be filled with DEPC treated H<sub>2</sub>O, so that the total reaction volume is 50 ul (RT) or 25 ul (no RT).

On a 96-well PCR reaction plate (PE part # N801-0560), 37.5 ul of master mix may be aliquoted (22.5 ul of no RT master mix), and the RNA sample added for a total reaction volume of 50ul (25 ul, no RT). Control samples are loaded into two or  
 10 even three different wells in order to have enough template for generation of a standard curve.

The wells are capped using strip well caps (PE part # N801-0935), placed in a plate, and spin briefly in a plate centrifuge (Beckman) to collect all volume in the bottom of the tubes. Generally, a short spin up to 500rpm in a Sorvall RT is  
 15 sufficient.

For the RT-PCR reaction, the following thermal profile may be used:

- 25°C for 10 min
- 48°C for 30 min
- 20      • 95°C for 5 min
- 4°C hold (for 1 hour)
- Store plate @-20°C or lower upon completion.

TaqMan reaction (Template comes from RT plate.)

A master mix may be prepared according to the following table:

TaqMan reaction (per well)	
<u>Reagent</u>	<u>Per Rx'n (in ul)</u>
TaqMan Master Mix	4.17
100 uM Probe	.025
100 uM	.05
Forward	
primer	
100 uM	.05
Reverse	
primer	
Template	-
DEPC H <sub>2</sub> O	18.21
Total	22.5

5

Appropriate forward, reverse, and probe primers may be designed for each protein tyrosine kinase biomarker polypeptides coding region for use in the RT-PCR reaction

10 Using a Gilson P-10 repeat pipetter, 22.5 ul of master mix is aliquoted per well of a 96-well optical plate. Then, using P-10 pipetter, 2.5 ul of sample is added to individual wells. Generally, RT samples are run in triplicate with each primer/probe set used, and no RT samples are run once and only with one primer/probe set, often gapdh (or other internal control).

15 A standard curve is then constructed and loaded onto the plate. The curve has five points plus one no template control (NTC, =DEPC treated H<sub>2</sub>O). The curve may be made with a high point of 50 ng of sample (twice the amount of RNA in unknowns), and successive samples of 25, 10, 5, and 1 ng. The curve may be made from a control sample(s) (see above).

20 The wells are capped using optical strip well caps (PE part # N801-0935), placed in a plate, and spun in a centrifuge to collect all volume in the bottom of the tubes. Generally, a short spin up to 500rpm in a Sorvall RT is sufficient.

Plates are loaded onto a PE 5700 sequence detector making sure the plate is aligned properly with the notch in the upper right hand corner. The lid may be tightened down and run using the 5700 and 5700 quantitation program and the SYBR probe using the following thermal profile:

5

- 50°C for 2 min
- 95°C for 10 min
- and the following for 40 cycles:
  - 95°C for 15 sec
  - 60°C for 1 min
- Change the reaction volume to 25ul.

10

Once the reaction may be complete, a manual threshold of around 0.1 may be set to minimize the background signal. Additional information relative to operation of the GeneAmp 5700 machine may be found in reference to the following manuals:

15 “GeneAmp 5700 Sequence Detection System Operator Training CD”; and the “User’s Manual for 5700 Sequence Detection System”; available from Perkin-Elmer and hereby incorporated by reference herein in their entirety.

The skilled artisan would acknowledge that modifications to the above protocol may be required for each protein tyrosine kinase biomarker polypeptide of the present invention. The skilled artisan would also acknowledge that cell lines other than A549 could be used and that A549 are only provided as an example. The skilled artisan would also acknowledge that other means may be used to assess the ability of a complimentary oligonucleotide, such as the RNAi reagents provided in SEQ ID

20 NO:534 to 557, which include, but are not limited to western blots and ELISA assays, among others.

25

EXAMPLE 6 – ALTERNATIVE METHOD OF ASSESSING ABILITY OF  
COMPLIMENTARY SEQUENCES TO MODULATE EXPRESSION LEVELS OF  
THE PROTEIN TYROSINE KINASE BIOMARKER POLYPEPTIDES OF THE  
PRESENT INVENTION.

30

Preferred complimentary sequences that may be assessed for their ability to modulate the expression levels the protein tyrosine kinase biomarker polypeptides of the present invention are provided as SEQ ID NO:534 to 557. Other complimentary sequences may be designed based upon the coding region of the protein tyrosine

5 kinase biomarker polypeptides of the present invention as provided as SEQ ID NO:1 thru 137, and are specifically contemplated by the present invention.

#### Co-Transfection RNAi

10 Transfection:

Day prior to transfection, seed  $2 \times 10^5$  HeLa cells per well of a 24 well dish. The following day, cells should be 90-95% confluent. Dilute 4.5uL of 20uM stock RNAi (one or more of SEQ ID NO:534 to 557) in 50uL Optimem in a polystyrene

15 tube for each RNAi to be transfected (tube A). Mix by gentle tapping. In another polystyrene tube combine 2uL Lipofectamine 2000 with 50 uL Optimem (tube B). Mix by gentle tapping. Allow to sit at RT for 5'. Combine 50uL tube B with the 50uL for each tube A. Mix by gentle tapping. Allow to sit at RT for 15'. Add 500uL serum/antibiotic-free MEM to each tube to give a final RNAi concentration of

20 150nM. (For cotransfections of RNAi with plasmid, use 1uL of 20uM stock RNAi (final concentration of 33nM) along with 1ug vector DNA in tube A, and then proceed with transfection protocol above). Remove the media from HeLa plates and replace with the 600uL transfection mix. Put in 37°C 5% CO2 incubator for 4-5 hours. Replace the media with MEM containing 10% FBS.

25 Controls to include in the transfection include a fluorescent oligonucleotide control (1U/uL=20uM) to calculate transfection efficiency, GFP B as a non-specific negative control, CDC2 as a normalizing knockdown control, and an untransfected control receiving no DNA.

30 Lysis:



48 hours post-transfection, aspirate media and wash cells 1X with approx. 500uL cold 1xPBS per well. Aspirate and replace with 100uL cold RIPA containing protease inhibitors (1 mini BM protease inhibitor tablet/10mL 1x RIPA). Rock and tap the plate a few times and place at 4<sup>0</sup>C for 10-15 minutes. Tap/rock the plate several more times. Using a 200uL pipetteman, aspirate 5-10 times and wash the well to ensure complete lysis and transfer of all material. Transfer lysate to an eppendorf tube and pipette up and down 5-10 times. If sample is still viscous, pipette up and down several more times. Spin samples down for 10' at 14000 RPM 4<sup>0</sup>C. Samples can now be stored at -20<sup>0</sup>C or prepared for loading.

10

Western blotting/Novex:

Prepare sample by combining 20uL lysate with 3uL reducing reagent and 7uL 4X gel loading dye. Heat at 70<sup>0</sup>C for 10' and then place samples on ice. While samples are heating, prepare desired gel (usually a 4-12% Bis-Tris gel) by removing comb and sealing tape. Place gels in gel box and fill inner and outer chambers with desired buffer (either 1x MES or MOPS- Add 50mL 20x buffer to 950mL dH2O for each gel box).. Add 600uL Oxidizing reagent to the inner chamber. Wash out each well by blasting with 500uL buffer. In well one, load 5uL marker- Invitrogen's SeeBlue Plus2. Load samples in subsequent lanes. Run gel at 200V for 45-50 minutes. Make up 1X transfer buffer- 50mL 20x transfer buffer, Methanol (100mL if transferring one gel, 200mL if transferring 2 gels in the same apparatus) and dH2O to 1000mL. Soak blotting pads in dH2O and then transfer buffer- make sure to push down on pads to rid of air bubbles. Soak precut Hybond-ECL membrane (Amersham nitrocellulose) in dH2O and then in transfer buffer. Cut the end off of Biorad filter paper to match size of transfer membrane. If transferring one gel, place 2 blotting pads into blotting chamber. For 2 gels, place down 1 pad. Briefly soak a filter paper in transfer buffer and carefully lay on blotting pad. Open gel cassette with cracking tool, cut off top, bottom and sides of gel. Briefly rinse it in transfer buffer and then lay it on filter paper carefully making sure no air bubbles are present. Lay transfer membrane on top again being careful there are no bubbles. Put down filter paper. Put down 2 blotting pads if transferring one gel to complete the sandwich. If transferring

25  
30

2, put down 1 blotting pad, filter paper, gel, membrane, filter paper, blotting pad. Gels are now ready for transfer. Squeeze together the gel sandwich and place in transfer apparatus. Fill inner and outer chambers with transfer buffers. Transfer gels for 1 hour at 30V.

- 5 Remove membranes and place them in Superblock (Pierce) and rock at RT for a minimum of 1 hour-overnight. (I have stored membranes in Superblock at 4<sup>0</sup>C over the weekend). Primary antibody and normalizing antibody are diluted in a 1:10 mix of Superblock:1xPBS/0.3% Tween-20. Membranes are incubated and rocked at RT in primary antibody for a minimum of 1 hour-overnight. Membranes are then
- 10 washed thoroughly in 1xPBS/0.3% Tween-20. I usually give several quick rinses and then rinse 3X 5' in 1xPBS/0.3% Tween-20. During the final wash, HRP-conjugated secondary antibody is diluted in 1xPBS/0.3% Tween-20. Add this to membrane and rock at RT for a minimum of 30'. Wash membranes thoroughly. I usually give several quick rinses and then rinse 3X 5' in 1xPBS/0.3% Tween-20. Membranes are
- 15 removed from wash buffer and the excess buffer drained by holding the edge of the membranes on a paper towel. Membranes are placed on Saran Wrap that has been smoothed on benchtop to remove air bubbles. Enough ECL reagent is added to cover the membrane for 1 minute. Remove membranes and drain off excess ECL on paper towel. Place membranes in between two transparency sheets, being careful to smooth
- 20 out air bubbles.

#### Quantitation:

- 25 Expose membranes using FluorS-Max. Relative percent inhibition may be determined by comparing the intensity of each band with RNAi treatment to the intensity of each band without RNAi treatment (control). Normalize lanes by dividing band of interest by normalizing band for each lane. Divide the normalized value for each treated sample by the normalized value of the control. Percent inhibition can then be calculated by using the formula (1-above value) x 100.

- 30 The skilled artisan would acknowledge that modifications to the above protocol may be required for each protein tyrosine kinase biomarker polypeptide of the present invention.

2, put down 1 blotting pad, filter paper, gel, membrane, filter paper, blotting pad. Gels are now ready for transfer. Squeeze together the gel sandwich and place in transfer apparatus. Fill inner and outer chambers with transfer buffers. Transfer gels for 1 hour at 30V.

- 5 Remove membranes and place them in Superblock (Pierce) and rock at RT for a minimum of 1 hour-overnight. (I have stored membranes in Superblock at 4<sup>0</sup>C over the weekend). Primary antibody and normalizing antibody are diluted in a 1:10 mix of Superblock:1xPBS/0.3% Tween-20. Membranes are incubated and rocked at RT in primary antibody for a minimum of 1 hour-overnight. Membranes are then
- 10 washed thoroughly in 1xPBS/0.3% Tween-20. I usually give several quick rinses and then rinse 3X 5' in 1xPBS/0.3% Tween-20. During the final wash, HRP-conjugated secondary antibody is diluted in 1xPBS/0.3% Tween-20. Add this to membrane and rock at RT for a minimum of 30'. Wash membranes thoroughly. I usually give several quick rinses and then rinse 3X 5' in 1xPBS/0.3% Tween-20. Membranes are
- 15 removed from wash buffer and the excess buffer drained by holding the edge of the membranes on a paper towel. Membranes are placed on Saran Wrap that has been smoothed on benchtop to remove air bubbles. Enough ECL reagent is added to cover the membrane for 1 minute. Remove membranes and drain off excess ECL on paper towel. Place membranes in between two transparency sheets, being careful to smooth
- 20 out air bubbles.

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- 25 determined by comparing the intensity of each band with RNAi treatment to the intensity of each band without RNAi treatment (control). Normalize lanes by dividing band of interest by normalizing band for each lane. Divide the normalized value for each treated sample by the normalized value of the control. Percent inhibition can then be calculated by using the formula (1-above value) x 100.

- 30 The skilled artisan would acknowledge that modifications to the above protocol may be required for each protein tyrosine kinase biomarker polypeptide of the present invention.

## BRIEF DESCRIPTION OF THE SEQUENCE LISTING

Incorporated herein by reference in its entirety is a Sequence Listing, comprising SEQ ID NO:1 through SEQ ID NO:557, which include nucleic acid and amino acid sequences of the protein tyrosine kinase biomarkers as presented in Table 2 herein and the nucleotide sequences of forward and reverse primer pairs for the polynucleotide markers, probes, and RNAi reagents as described herein. The Sequence Listing is contained on a compact disc, i.e., CD-ROM, three identical copies of which are filed herewith. The Sequence Listing, in IBM/PC MS-DOS text format, was first created on August 25, 2003, and is 896 KB in size.

10

The contents of all patents, patent applications, published PCT applications and articles, books, references, reference manuals, abstracts, the Sequence Listing, and internet websites cited herein are hereby incorporated by reference in their entirety to more fully describe the state of the art to which the invention pertains.

15

As various changes can be made in the above-described subject matter without departing from the scope and spirit of the present invention, it is intended that all subject matter contained in the above description, or defined in the appended claims, be interpreted as descriptive and illustrative of the present invention. Many modifications and variations of the present invention are possible in light of the above teachings.

20

## WHAT IS CLAIMED IS:

1. A predictor set comprising a plurality of polynucleotides whose expression pattern is predictive of the response of cells to treatment with a compound that modulates protein tyrosine kinase activity or members of the protein tyrosine kinase pathway.  
5
2. The predictor set according to claim 1 wherein the polynucleotides are selected from the group consisting of:
  - a.) the polynucleotides provided in Table 2;
  - b.) the sensitive predictor polynucleotides provided in  
10 Table 2; and
  - c.) the resistant predictor polynucleotides provided in Table 2.
3. The predictor set according to claim 2 wherein the plurality of  
15 polynucleotides comprise the number of polynucleotides selected from the group consisting of:
  - a.) at least about 1 polynucleotides;
  - b.) at least about 3 polynucleotides;
  - c.) at least about 5 polynucleotides;
  - 20 d.) at least about 7 polynucleotides;
  - e.) at least about 10 polynucleotides;
  - f.) at least about 15 polynucleotides;
  - g.) at least about 20 polynucleotides;
  - h.) at least about 25 polynucleotides; and
  - 25 i.) at least about 30 polynucleotides.
4. The predictor set according to claim 3 wherein the plurality of polynucleotides comprise a member of the group consisting of:
  - a.) the polynucleotides provided in Table 3;
  - 30 b.) the sensitive predictor polynucleotides provided in Table 3;

- 5
- c.) the resistant predictor polynucleotides provided in Table 3;
  - d.) the polynucleotides provided in Table 4;
  - e.) the sensitive predictor polynucleotides provided in Table 4;
  - f.) the resistant predictor polynucleotides provided in Table 4;
  - g.) the polynucleotides provided in Table 5;
  - h.) the sensitive predictor polynucleotides provided in Table 5; and
  - 10 i.) the resistant predictor polynucleotides provided in Table 5.

15 5. The predictor set according to claim 4 wherein the compound is selected from the group consisting of:

- a.) antisense reagents directed to said polynucleotides;
- b.) antibodies directed against polypeptides encoded by said polynucleotides; and
- c.) small molecule compounds.

20 6. The predictor set according to claim 5 wherein the compound is BMS-A.

7. The predictor set according to claim 1 wherein said cells are a member of the group consisting of: breast cells, and breast cancer cells.

25 8. A predictor set comprising a plurality of polypeptides whose expression pattern is predictive of the response of cells to treatment with compounds that modulate protein tyrosine kinase activity or members of the protein tyrosine kinase pathway.

9. The predictor set according to claim 8 wherein the polypeptides are selected from the group consisting of:

- 30
- a.) the polypeptides provided in Table 2;
  - b.) the sensitive predictor polypeptides provided in Table 2; and

c.) the resistant predictor polypeptides provided in Table 2.

10. The predictor set according to claim 9 wherein the plurality of polypeptides comprise the number of polypeptides selected from the group consisting of:

5

- a.) at least about 1 polypeptides;
- b.) at least about 3 polypeptides;
- c.) at least about 5 polypeptides;
- d.) at least about 7 polypeptides;
- 10 e.) at least about 10 polypeptides;
- f.) at least about 15 polypeptides;
- g.) at least about 20 polypeptides;
- h.) at least about 25 polypeptides; and
- i.) at least about 30 polypeptides.

15

11. The predictor set according to claims 10 wherein the plurality of polypeptides comprise a member of the group consisting of:

20

- a.) polypeptides provided in Table 3;
- b.) the sensitive predictor polypeptides provided in Table 3;
- c.) the resistant predictor polypeptides provided in Table 3;
- d.) the polypeptides provided in Table 4;
- e.) the sensitive predictor polypeptides provided in Table 4;
- f.) the resistant predictor polypeptides provided in Table 4;
- g.) the polypeptides provided in Table 5;
- h.) the sensitive predictor polypeptides provided in Table 5;
- 25 and
- i.) the resistant predictor polypeptides provided in Table 5.

12. The predictor set according to claim 11 wherein the compound is selected from the group consisting of:

30

- a.) antisense reagents directed against polynucleotides encoding said polypeptides;
- b.) antibodies directed against said polypeptides; and

c.) small molecule compounds.

13. The predictor set according to claim 12 wherein the compound is BMS-A.

5 14. The predictor set according to claim 8 wherein said cells are a member of the group consisting of: breast cells, and breast cancer cells.

15. A method for predicting whether a compound is capable of modulating the activity of cells, comprising the steps of:

- 10 a.) obtaining a sample of cells;  
b.) determining whether said cells express a plurality of markers; and  
c.) correlating the expression of said markers to the compounds ability to modulate the activity of said cells.

15 16. The method according to claim 15 wherein the plurality of markers are polynucleotides.

17. The method according to claim 16 wherein the polynucleotides are the polynucleotides of claim 4.

20 18. The method according to claim 17 wherein the compounds are a member of the group consisting of:

- a.) the compounds according to claim 5; and  
b.) the compounds according to claim 6.

25 19. The method according to claim 18 wherein the cells are a member of the group consisting of: breast cells, and breast cancer cells.

20. The method according to claim 15 wherein the plurality of markers are polypeptides.

21. The method according to claim 20 wherein the polypeptides are the polypeptides of claim 11.

30 22. The method according to claim 21 wherein the compounds are a member of the group consisting of:

- c.) the compounds according to claim 12; and



d.) the compounds according to claim 13.

23. The method according to claim 19 wherein the cells are a member of the group consisting of: breast cells, and breast cancer cells.
- 5           24. A plurality of cell lines for identifying polynucleotides and polypeptides whose expression levels correlate with compound sensitivity or resistance of cells associated with a disease state.
- 10           25. The plurality of cell lines according to claim 24 wherein said cell lines are breast cancer cell lines.
26. The plurality of cell lines according to claim 25 wherein said cell lines comprise one or more cell lines provided in Table 1.
- 15           27. A method of identifying polynucleotides and polypeptides that predict compound sensitivity or resistance of cells associated with a disease state, comprising the steps of:
- a.) subjecting the plurality of cell lines according to claim 26 to one or more compounds;
- 20           b.) analyzing the expression pattern of a microarray of polynucleotides or polypeptides; and
- c.) selecting polynucleotides or polypeptides that predict the sensitivity or resistance of cells associated with a disease state by using said expression pattern of said microarray.
- 25           28. The method according to claim 24 wherein the compounds are a member of the group consisting of:
- a.) the compounds according to claim 5; and
- b.) the compounds according to claim 6;
- c.) the compounds according to claim 12; and
- 30           d.) the compounds according to claim 13.

29. The method according to claim 29 wherein said disease is breast cancer.

30. A method for predicting whether an individual requiring treatment for  
5 a disease state, will successfully respond or will not respond to said treatment comprising the steps of:

- a.) obtaining a sample of cells from said individual;
- b.) determining whether said cells express a plurality of  
markers; and
- 10 c.) correlating the expression of said markers to the individuals  
ability to respond to said treatment.

31. The method according to claim 30 wherein the plurality of markers are polynucleotides.

15 32. The method according to claim 31 wherein the polynucleotides are the polynucleotides of claim 4.

33. The method according to claim 32 wherein the compounds are a member of the group consisting of:

- a.) the compounds according to claim 5; and
- 20 b.) the compounds according to claim 6.

34. The method according to claim 33 wherein the disease state is breast cancer.

25 35. The method according to claim 30 wherein the plurality of markers are polypeptides.

36. The method according to claim 35 wherein the polypeptides are the polypeptides of claim 11.

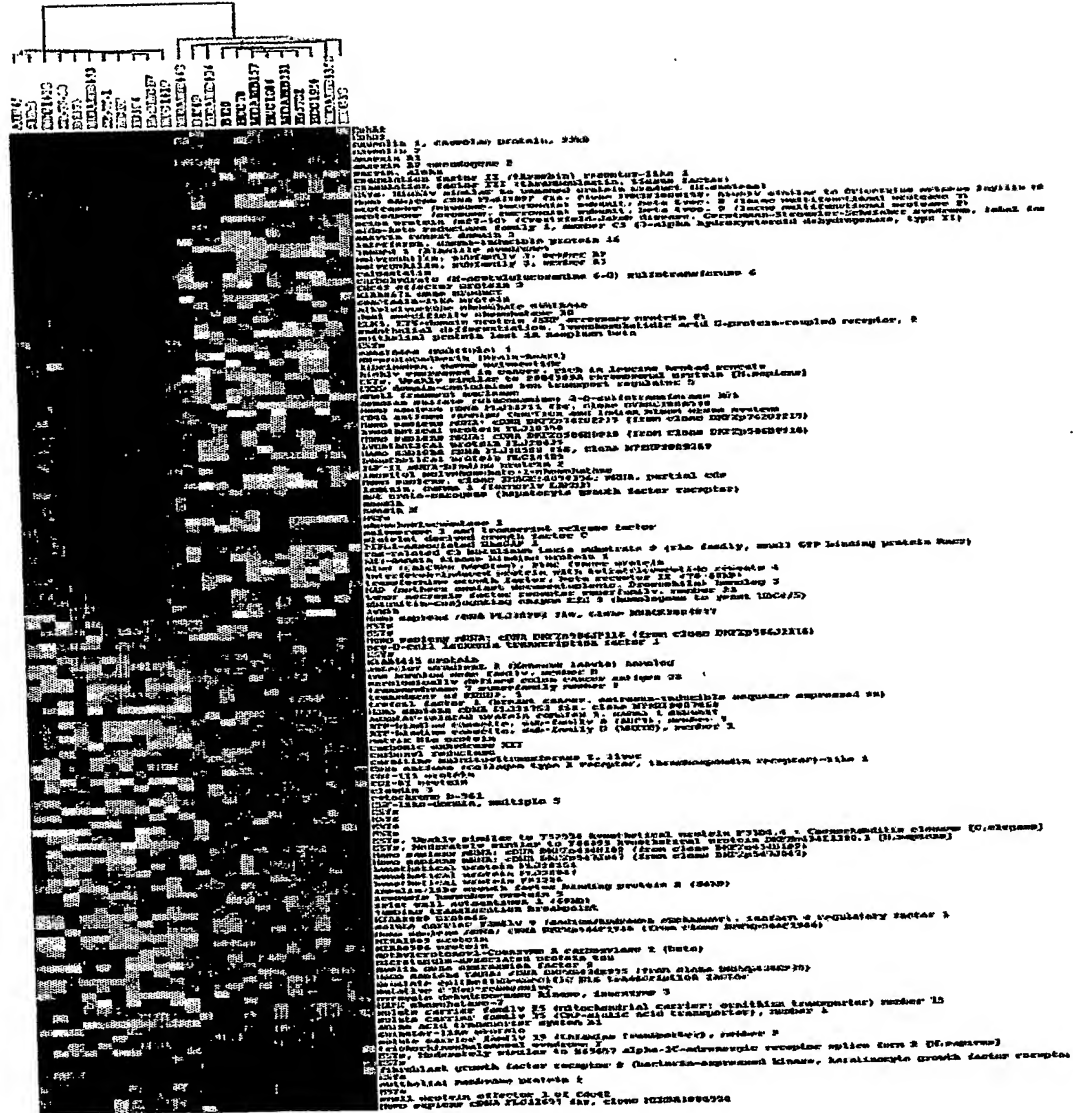
37. The method according to claim 36 wherein the compounds are a member of the group consisting of:

- 30 a.) the compounds according to claim 5; and
- b.) the compounds according to claim 6.

38. The method according to claim 37 wherein the disease state is breast cancer.
39. A method of screening for candidate compounds capable of binding to and/or modulating the activity of a protein tyrosine kinase biomarker polypeptide, comprising:
- 5 (a) contacting a test compound with a polypeptide according to claim 11; and
- (b) selecting as candidate compounds those test compounds that bind to and/or modulate activity of the polypeptide.
- 10 40. A method of treating breast cancer in a subject, comprising administering a modulator of one or more protein tyrosine kinase biomarker polypeptides, wherein said polypeptide(s) is selected from the group consisting of:
- 15 a.) polypeptides provided in Table 2;
- b.) the sensitive predictor polypeptides provided in Table 2;
- c.) the resistant predictor polypeptides provided in Table 2;
- d.) polypeptides provided in Table 3;
- e.) the sensitive predictor polypeptides provided in Table 3;
- f.) the resistant predictor polypeptides provided in Table 3;
- g.) the polypeptides provided in Table 4;
- 20 h.) the sensitive predictor polypeptides provided in Table 4;
- i.) the resistant predictor polypeptides provided in Table 4;
- j.) the polypeptides provided in Table 5; and
- k.) the sensitive predictor polypeptides provided in Table 5.

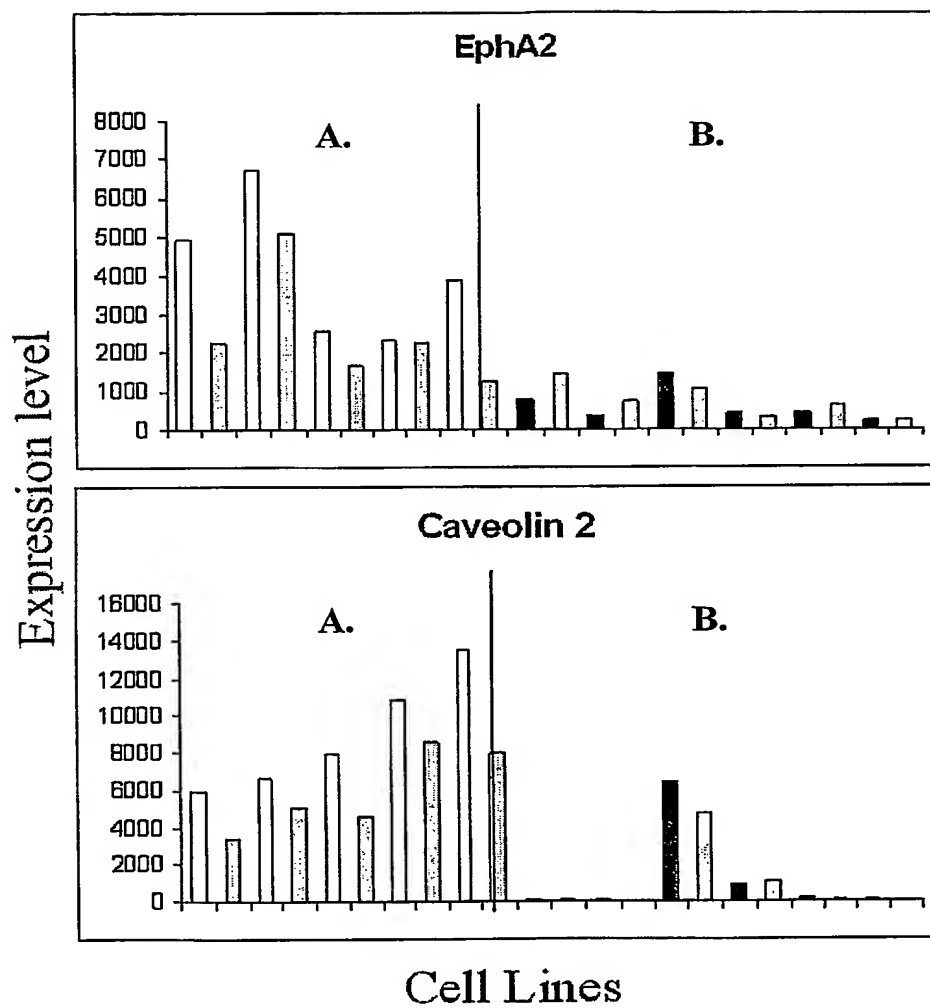
1/7

FIG. 1



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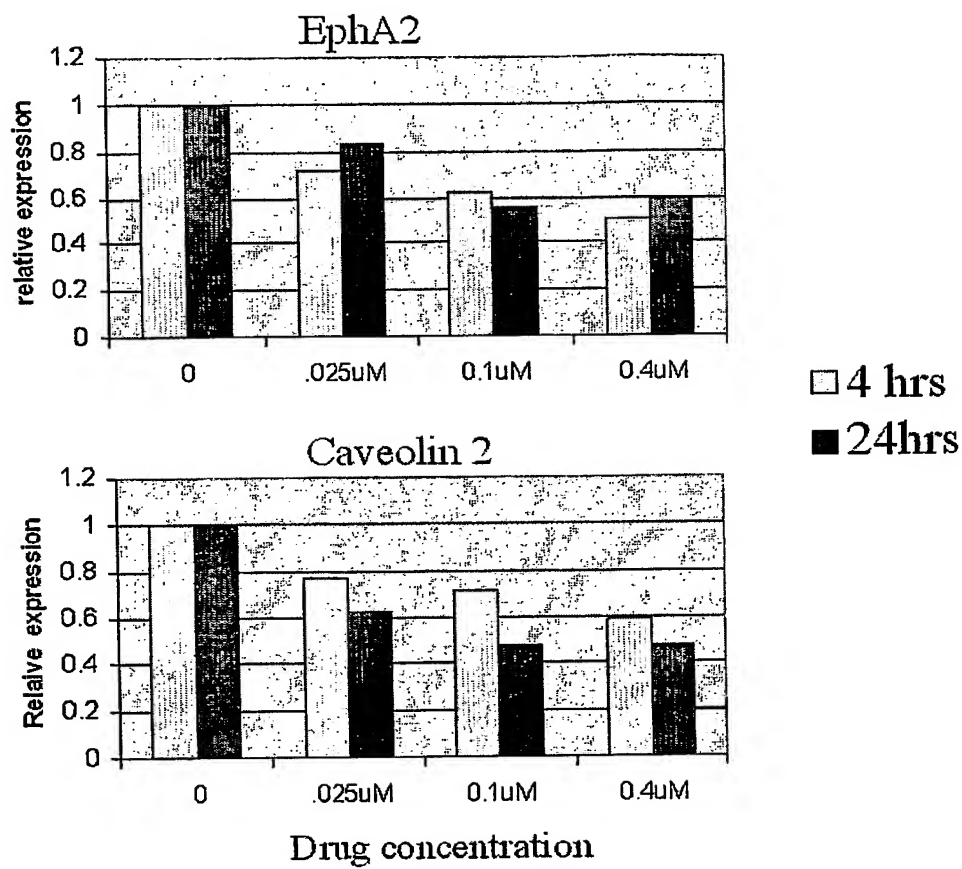
FIG. 2



- A. | ☐ Sensitive control  
☐ Sensitive+BMS-A
- B. | ☒ Resistant control  
☐ Resistant +BMS-A

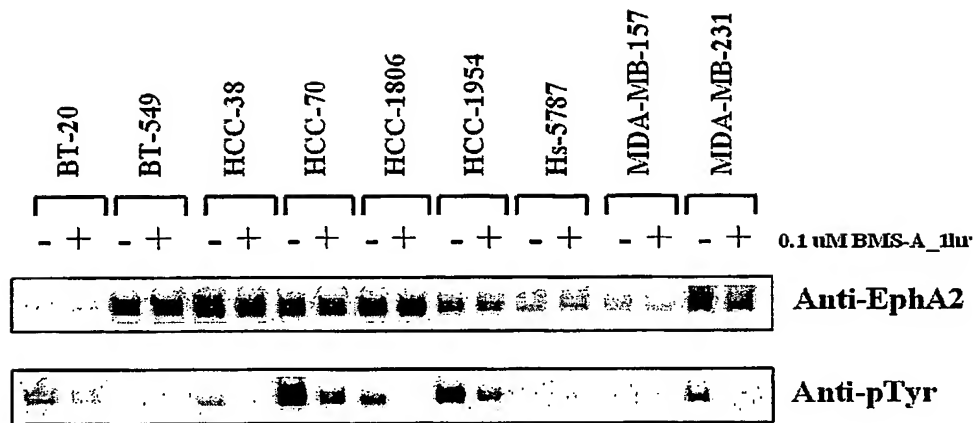
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FIG. 3



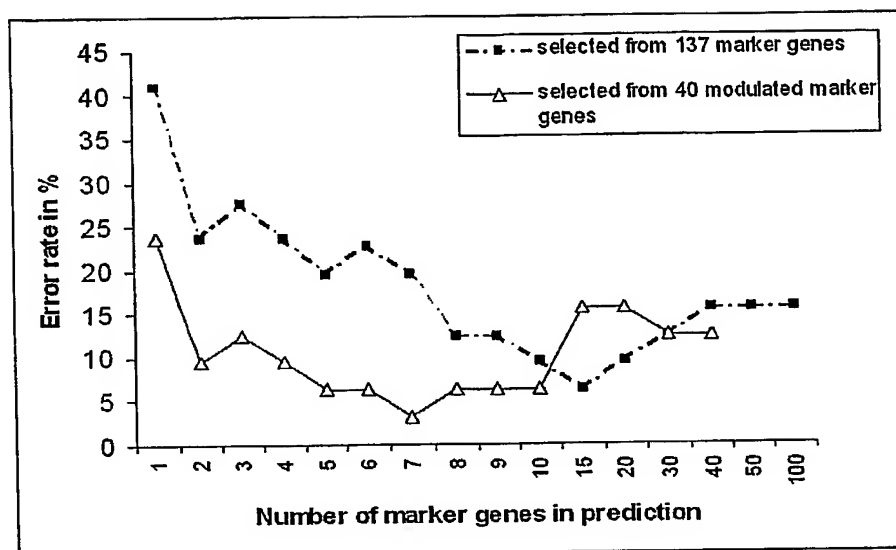
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FIG. 4



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FIG. 5





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FIG. 6

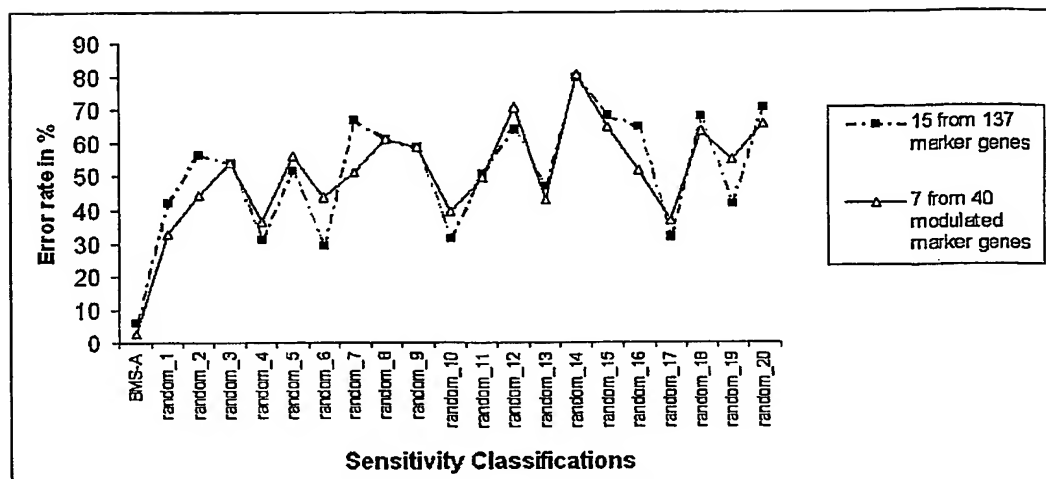
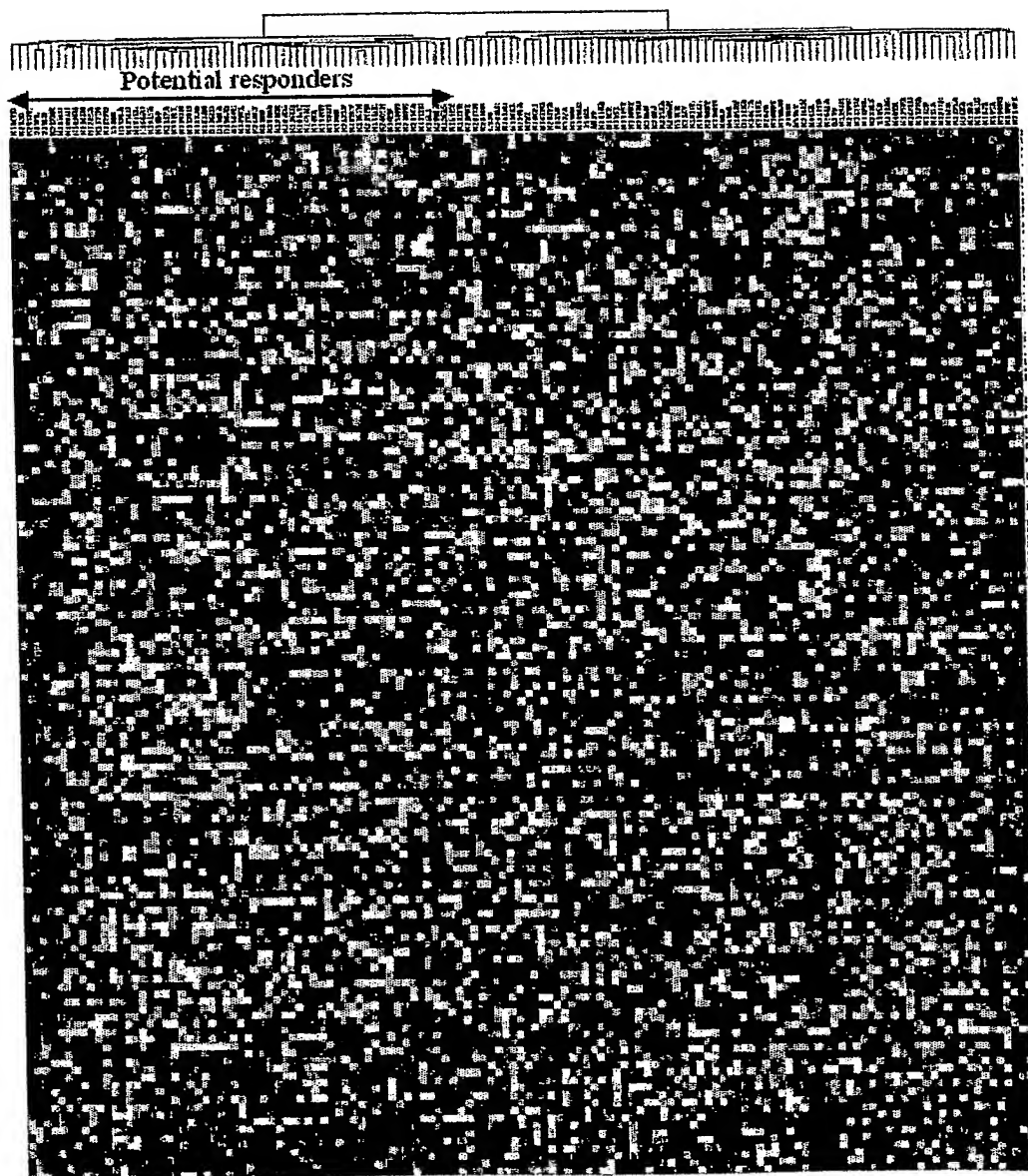


FIG. 7



## SEQUENCE LISTING

<110> Bristol-Myers Squibb Company

<120> IDENTIFICATION OF GENES FOR PREDICTING ACTIVITY OF COMPOUNDS THAT INTERACT WITH AND/OR MODULATE PROTEIN TYROSINE KINASES AND/OR PROTEIN TYROSINE KINASE PATHWAYS IN BREAST CELLS

<130> D0273 PCT

<150> 60/406,385

<151> 2002-08-27

<160> 557

<170> PatentIn version 3.2

<210> 1

<211> 3921

<212> DNA

<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<210> 36
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<212> DNA
<213> Homo sapiens

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ccctctcaat ttcttaaaca acaacaaaaa aatgcttgaa gattgtcttt gagtgtgaaga 540  
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 <212> DNA  
 <213> Homo sapiens

<220>  
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 <222> (21)..(21)  
 <223> n is a, c, g, or t

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<212> DNA
<213> Homo sapiens

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 <212> DNA  
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 <212> DNA  
 <213> Homo sapiens

<400> 66  
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<210> 67
<211> 1216
<212> DNA
<213> Homo sapiens

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 aataaacatg ctccctg 1216

<210> 68  
 <211> 2201  
 <212> DNA  
 <213> Homo sapiens

<400> 68  
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<210> 69  
<211> 1219  
<212> DNA  
<213> Homo sapiens

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<210> 70
<211> 482
<212> DNA
<213> Homo sapiens

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tatttattgt aagaatgctt atcatgaaga tacacactgt aactacaaga aattataaat 420
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aa 482

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<210> 71

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<211> 456  
 <212> DNA  
 <213> Homo sapiens

<400> 71  
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<210> 72  
 <211> 2278  
 <212> DNA  
 <213> Homo sapiens

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<210> 73  
 <211> 1819  
 <212> DNA  
 <213> Homo sapiens

<400> 73  
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<212> DNA

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 <213> Homo sapiens

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<211> 1250

<212> DNA

<213> Homo sapiens

<400> 93

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<212> DNA  
<213> Homo sapiens

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<210> 97  
 <211> 962  
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caagtctttg caatctgggt catccaaagg tatctcaaag aatgagcgtt ttgttgga	900
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<210> 98  
 <211> 528  
 <212> DNA  
 <213> Homo sapiens

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 <212> DNA  
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<210> 101  
 <211> 950  
 <212> DNA  
 <213> Homo sapiens

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 <211> 961  
 <212> DNA  
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 agaaagtctc tgcagccaga tagtacatgg tgtctccaca aaactaggca ttctggagat 240  
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<210> 103
<211> 405
<212> DNA
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<212> DNA
<213> Homo sapiens

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<212> DNA  
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 <212> DNA  
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 <211> 1433  
 <212> DNA  
 <213> Homo sapiens

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<210> 108  
 <211> 1825  
 <212> DNA  
 <213> Homo sapiens

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 <211> 1427  
 <212> DNA  
 <213> Homo sapiens

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 tttcctgccc cttctcccca aatcatcaac aatagaagaa gaagaaaaca tgtcaggaca 180  
 caaatgcagt tatccctggg acttacagga tcgatatgct caagataagt cagttgtaaa 240

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ttcaattcag agaacctgtc tggacttatc gaaagcaatt gtactctatc aaaagaggat    420
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<210> 110
<211> 823
<212> DNA
<213> Homo sapiens

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<400> 110
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gactaggcct caggcagaga ctaaaggaca tctcttgggg tgtcctgaag tgatttggac    180
ccctgagggc agacacctaa gtaggaatcc cagtgggaag caaagccata aggaagccca    240
ggattccttg tgatcaggaa gtgggcccagg aaggtctgta ccagctcaca tctcaactgc    300

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cacttggggtc tccagatttt ctgttacgtc cttgtgggtc aggatatttc tgggaagtcac    480
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<210> 111
<211> 553
<212> DNA
<213> Homo sapiens

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<220>
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<222> (498)..(498)
<223> n is a, c, g, or t

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gttccctttg cacaccggca cctcatcaca acaccctctt ggtgtggatg ccatgggggc    180
atgctgtagt caaaagttaa atgaaaaacc acaagtttag tttgactccg tctcctaggg    240
tggatttcat tcagatattt gttccatatt ataggagggt ggatcctagc aaggcaacag    300
tgtagttttt acattcacag attggctgaa gtagtacaaa ttgagctgct aatctaggtg    360
tctccctccc tgttaccata cttcataaga aatgtgaatt aaaatgaaca atggaccaca    420
ggtgggttata aaaatagata actcgagag tccataaata tctacagtta gtagagccag    480
aacttccaaa atttacnntt tttccataat ggtgcagaat atccccaagt atggttccaa    540
gaggacacag tca                        553

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<210> 112
<211> 425
<212> DNA
<213> Homo sapiens

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<220>  
 <221> misc\_feature  
 <222> (388)..(388)  
 <223> n is a, c, g, or t

<220>  
 <221> misc\_feature  
 <222> (417)..(417)  
 <223> n is a, c, g, or t

<400> 112  
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 gtgcc 425

<210> 113  
 <211> 544  
 <212> DNA  
 <213> Homo sapiens

<400> 113  
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 gccg 544

<210> 114

<211> 507  
 <212> DNA  
 <213> Homo sapiens

<400> 114  
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 ttcacagtga aaataatgca tgtcagtact aaaatagagt tgcttggttc cctgaaggaa 180  
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 tagtttgga actcgttct tgttacatac aaagccatta gcaaaaatat gtaacaaaat 420  
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<210> 115  
 <211> 4790  
 <212> DNA  
 <213> Homo sapiens

<400> 115  
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&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 127

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<213> Homo sapiens

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 tgcaggcggc ccaggccacc atgacacctc ccaccattct ctgctgcacg gccttcttca 360  
 tcttcgtgct ccagctcttc cgctgaagc agggagagag gtttgtccta acctccatca 420  
 tccagcta atgtcatgtctg tgtgtcatga ttgcggcctc catttataca gacaggcgtg 480  
 aagacattca cgacaaaaac gcgaaattct atcccgtagc cagagaaggc agctacggct 540  
 actcctacat cctggcgtgg gtggccttcg cctgcacctt catcagcggc atgatgtacc 600  
 tgatactgag gaagcgcaaa tagagttccg gagctgggtt gcttctgctg cagtacagaa 660  
 tccacattca gataaccatt ttgtatataa tcattattht ttgaggttht tctagcaaac 720  
 gtattgttht ctttaaaagc caaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaagaa 780  
 aaaaaaaaaa aaaaaaaaaa 799

<210> 135  
 <211> 561  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (368)..(368)  
 <223> n is a, c, g, or t

<400> 135  
 ttttaggaca aataaaatth atthttctct gtaaattcat ttaaaagtat gttatctatg 60  
 attatctat caagggcaga aatgttagat ctactccaa gataggtaaa cgcctttgaa 120

```

acgcaacaaa aagagacgat gatcttatga gctcatttat gttcatgCGT gaaagtgtga      180
aggtcactag ctttgctgtg tttctacaag tttccttgac tgtaaaaaca gtcaaaatgt      240
aaccaacctt attcaagatg ttaaattaat taagttaaataaaaattagcc aaagcactgt      300
aaattaaatg acataataact taagttctgt actgatgaca ccctttgatc aaaagaaggt      360
ggacccanta aggtgcttct ggagggttatt acttctcttaa ttccgaattt atcatcactg      420
actctttagg cataataaaa tgtagagtgt aaatagggtg gtgacaattt atttaattta      480
ggttgagcta cttataaata cctgagagct ctggaaacaa catatatatc catcttgcaa      540
atatcagtaa aaagaacaag t                                              561

```

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<210> 136
<211> 567
<212> DNA
<213> Homo sapiens

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<220>
<221> misc_feature
<222> (61)..(61)
<223> n is a, c, g, or t

```

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<220>
<221> misc_feature
<222> (432)..(432)
<223> n is a, c, g, or t

```

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<220>
<221> misc_feature
<222> (441)..(441)
<223> n is a, c, g, or t

```

```

<220>
<221> misc_feature
<222> (465)..(465)
<223> n is a, c, g, or t

```

```

<220>
<221> misc_feature
<222> (495)..(495)
<223> n is a, c, g, or t

```

```

<220>
<221> misc_feature
<222> (501)..(501)
<223> n is a, c, g, or t

```

```

<220>
<221> misc_feature
<222> (532)..(532)

```



<223> n is a, c, g, or t

<220>

<221> misc\_feature

<222> (559)..(559)

<223> n is a, c, g, or t

<400> 136

tttttttaag agaacctgaa ttaaattttt aatattttta	aaaaggaaag ttgctgggaa	60
ntggtaaaca gaaacagaag attagaggcc taactagaaa	gagacactgg tgtagcaga	120
gagatattga ggggctgtaa gctaaagggt tgaaatctaa	agatagagtg gaaaaggag	180
taggcacccc caccagcccc tgcttgacat ctgctttagt	tcattccagc aggaaggagg	240
agaagggcag ggaggtaggg agcttctcag caaagccagc	ttcagctttg ataatctcac	300
ccacctaccc catttaagga gttccagggt taagagttta	aaaacagggt gcaccagacc	360
atcattcagg agacaggaac tcattccagg ttcctaagag	aactcctatc tcagacctga	420
aggggtttcc anggettcag nttgagctcc tctgggctaa	ccagnagtca cttgattaag	480
tcccgtgcc ttgancccat nttccaggag ggggctattg	cccgaggag tntaaggag	540
ttccagcccc caagccttnt taggcac		567

<210> 137

<211> 1551

<212> DNA

<213> Homo sapiens

<400> 137

aaaacatggt gateccaatg atgtgatcac ttttgaacct	ttccattaca aagcattgta	60
tagataaact tttaattcag taggaggaga aagttcattc	ttggcctggt ggctttgatt	120
attatgggta ctttaaagtc agtatattatc aagaaagga	acttgaccac cattggcaca	180
tgtgacattt aagctcttca gccttttctt ttttagttgt	aggtgtttac atttcatttc	240
taagccaact ctgtatttat gagagaagtt taagccttac	atcatttgat actaaagggt	300
tatttgtggt aatgaaaaa tgaccocaaa attacagagg	aatatgccag tttaagaaat	360
ggctacttaa agttgcttct ctctttcctt ctactcatg	aaattaattg gtcttcttca	420
agtttcttta gattccatta aatgattaaa tctatttaa	gagccattca tcaacgtgat	480
ttgtgtgtta gccaatgaat ctgtctcagc ttttgaccaa	atgggtttta gacaaatgca	540
aagatctgcc tctagtccat atggctcttt ttgagtgcta	gtattttgca tttcacataa	600
tgtagtattt ttgagctttt aaagagagca tttagacaaa	gaagcaaaga gaggaaggga	660

```

ccaatcaact catcagttcc atgcatcaac aaagcatagc tagtagagga atataaatga      720
cagattgaca aactgtagga aacactgtta ctctctttct gaagttttca agcaccatcc      780
tatgtgaaag ttccctcctg tccaaacaag ctcaaggccc atcttctccc tatacaaggc      840
aaacctgtaa ggccttcctt ccaaagagta cattgctttg gttttcttcc taaattccta      900
ttggaattag aactctcaga atccctggga gacagagcaa agatgactta attcattgag      960
cagcagagct ccctataagt gaacatcacc ttcccatctt ttcttactgc cacaccata      1020
cgagagagga tctagaaaga gcgatggcag cctgaacaca gaaaacaccc ccacttggca      1080
gacctctcct cagcaatccc ccagcctca tgcttcactt gcaaagtgtg acataaccac      1140
gggacgagtg ccttgcttga accaaagcaa cgatttagcc agtctggacc tctctgtgct      1200
ttttttaatt cttcctgtga atacctcagc ttcaactggg cctccataca gtcagttggt      1260
gggcttattg tactgtggtg ctttgcaatg caaccctgca aagaacaaga tttgtactaa      1320
taccaaaggt tctttctcta tgtctctccc tctgcctccc tcgttcttcc cttttttcta      1380
gttcttcacg gttccaaagc tttactatga acctgggcat gttggcaatg cagaccgcgc      1440
aattccttac cgaattttct cagatatacc tcatagacaa tagtgtttag agtaatgtta      1500
ttatagcgta tgtaataaat tattcactgt ttcttttggt aactgtgatt t              1551

```

<210> 138  
 <211> 976  
 <212> PRT  
 <213> Homo sapiens

<400> 138

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Met Glu Leu Gln Ala Ala Arg Ala Cys Phe Ala Leu Leu Trp Gly Cys
1      5      10      15

```

```

Ala Leu Ala Ala Ala Ala Ala Gln Gly Lys Glu Val Val Leu Leu
20      25      30

```

```

Asp Phe Ala Ala Ala Gly Gly Glu Leu Gly Trp Leu Thr His Pro Tyr
35      40      45

```

```

Gly Lys Gly Trp Asp Leu Met Gln Asn Ile Met Asn Asp Met Pro Ile
50      55      60

```

```

Tyr Met Tyr Ser Val Cys Asn Val Met Ser Gly Asp Gln Asp Asn Trp
65      70      75      80

```

Leu Arg Thr Asn Trp Val Tyr Arg Gly Glu Ala Glu Arg Asn Asn Phe  
85 90 95

Glu Leu Asn Phe Thr Val Arg Asp Cys Asn Ser Phe Pro Gly Gly Ala  
100 105 110

Ser Ser Cys Lys Glu Thr Phe Asn Leu Tyr Tyr Ala Glu Ser Asp Leu  
115 120 125

Asp Tyr Gly Thr Asn Phe Gln Lys Arg Leu Phe Thr Lys Ile Asp Thr  
130 135 140

Ile Ala Pro Asp Glu Ile Thr Val Ser Ser Asp Phe Glu Ala Arg His  
145 150 155 160

Val Lys Leu Asn Val Glu Glu Arg Ser Val Gly Pro Leu Thr Arg Lys  
165 170 175

Gly Phe Tyr Leu Ala Phe Gln Asp Ile Gly Ala Cys Val Ala Leu Leu  
180 185 190

Ser Val Arg Val Tyr Tyr Lys Lys Cys Pro Glu Leu Leu Gln Gly Leu  
195 200 205

Ala His Phe Pro Glu Thr Ile Ala Gly Ser Asp Ala Pro Ser Leu Ala  
210 215 220

Thr Val Ala Gly Thr Cys Val Asp His Ala Val Val Pro Pro Gly Gly  
225 230 235 240

Glu Glu Pro Arg Met His Cys Ala Val Asp Gly Glu Trp Leu Val Pro  
245 250 255

Ile Gly Gln Cys Leu Cys Gln Ala Gly Tyr Glu Lys Val Glu Asp Ala  
260 265 270

Cys Gln Ala Cys Ser Pro Gly Phe Phe Lys Phe Glu Ala Ser Glu Ser  
275 280 285

Pro Cys Leu Glu Cys Pro Glu His Thr Leu Pro Ser Pro Glu Gly Ala  
290 295 300

Thr Ser Cys Glu Cys Glu Glu Gly Phe Phe Arg Ala Pro Gln Asp Pro  
 305 310 315 320

Ala Ser Met Pro Cys Thr Arg Pro Pro Ser Ala Pro His Tyr Leu Thr  
 325 330 335

Ala Val Gly Met Gly Ala Lys Val Glu Leu Arg Trp Thr Pro Pro Gln  
 340 345 350

Asp Ser Gly Gly Arg Glu Asp Ile Val Tyr Ser Val Thr Cys Glu Gln  
 355 360 365

Cys Trp Pro Glu Ser Gly Glu Cys Gly Pro Cys Glu Ala Ser Val Arg  
 370 375 380

Tyr Ser Glu Pro Pro His Gly Leu Thr Arg Thr Ser Val Thr Val Ser  
 385 390 395 400

Asp Leu Glu Pro His Met Asn Tyr Thr Phe Thr Val Glu Ala Arg Asn  
 405 410 415

Gly Val Ser Gly Leu Val Thr Ser Arg Ser Phe Arg Thr Ala Ser Val  
 420 425 430

Ser Ile Asn Gln Thr Glu Pro Pro Lys Val Arg Leu Glu Gly Arg Ser  
 435 440 445

Thr Thr Ser Leu Ser Val Ser Trp Ser Ile Pro Pro Pro Gln Gln Ser  
 450 455 460

Arg Val Trp Lys Tyr Glu Val Thr Tyr Arg Lys Lys Gly Asp Ser Asn  
 465 470 475 480

Ser Tyr Asn Val Arg Arg Thr Glu Gly Phe Ser Val Thr Leu Asp Asp  
 485 490 495

Leu Ala Pro Asp Thr Thr Tyr Leu Val Gln Val Gln Ala Leu Thr Gln  
 500 505 510

Glu Gly Gln Gly Ala Gly Ser Lys Val His Glu Phe Gln Thr Leu Ser  
 515 520 525

Pro Glu Gly Ser Gly Asn Leu Ala Val Ile Gly Gly Val Ala Val Gly

530		535		540											
Val 545	Val 545	Leu 545	Leu 545	Leu 545	Val 550	Leu 550	Ala 550	Gly 550	Val 555	Gly 555	Phe 555	Phe 555	Ile 555	His 555	Arg 560
Arg 565	Arg 565	Lys 565	Asn 565	Gln 565	Arg 565	Ala 565	Arg 565	Gln 570	Ser 570	Pro 570	Glu 570	Asp 570	Val 570	Tyr 575	Phe 575
Ser 580	Lys 580	Ser 580	Glu 580	Gln 580	Leu 580	Lys 580	Pro 585	Leu 585	Lys 585	Thr 585	Tyr 585	Val 585	Asp 590	Pro 590	His 590
Thr 595	Tyr 595	Glu 595	Asp 595	Pro 595	Asn 595	Gln 595	Ala 600	Val 600	Leu 600	Lys 600	Phe 600	Thr 605	Thr 605	Glu 605	Ile 605
His 610	Pro 610	Ser 610	Cys 610	Val 610	Thr 610	Arg 615	Gln 615	Lys 615	Val 615	Ile 615	Gly 620	Ala 620	Gly 620	Glu 620	Phe 620
Gly 625	Glu 625	Val 625	Tyr 625	Lys 625	Gly 630	Met 630	Leu 630	Lys 630	Thr 635	Ser 635	Ser 635	Gly 635	Lys 635	Lys 635	Glu 640
Val 645	Pro 645	Val 645	Ala 645	Ile 645	Lys 645	Thr 645	Leu 645	Lys 645	Ala 650	Gly 650	Tyr 650	Thr 650	Glu 650	Lys 655	Gln 655
Arg 660	Val 660	Asp 660	Phe 660	Leu 660	Gly 660	Glu 660	Ala 665	Gly 665	Ile 665	Met 665	Gly 665	Gln 665	Phe 670	Ser 670	His 670
His 675	Asn 675	Ile 675	Ile 675	Arg 675	Leu 675	Glu 675	Gly 680	Val 680	Ile 680	Ser 680	Lys 680	Tyr 685	Lys 685	Pro 685	Met 685
Met 690	Ile 690	Ile 690	Thr 690	Glu 690	Tyr 690	Met 695	Glu 695	Asn 695	Gly 695	Ala 695	Leu 700	Asp 700	Lys 700	Phe 700	Leu 700
Arg 705	Glu 705	Lys 705	Asp 705	Gly 705	Glu 710	Phe 710	Ser 710	Val 710	Leu 710	Gln 715	Leu 715	Val 715	Gly 715	Met 715	Leu 720
Arg 725	Gly 725	Ile 725	Ala 725	Ala 725	Gly 725	Met 725	Lys 725	Tyr 725	Leu 730	Ala 730	Asn 730	Met 730	Asn 730	Tyr 735	Val 735
His 740	Arg 740	Asp 740	Leu 740	Ala 740	Ala 740	Arg 740	Asn 745	Ile 745	Leu 745	Val 745	Asn 745	Ser 745	Asn 750	Leu 750	Val 750
Cys 755	Lys 755	Val 755	Ser 755	Asp 755	Phe 755	Gly 755	Leu 760	Ser 760	Arg 760	Val 760	Leu 760	Glu 765	Asp 765	Asp 765	Pro 765

Glu Ala Thr Tyr Thr Thr Ser Gly Gly Lys Ile Pro Ile Arg Trp Thr  
 770 775 780

Ala Pro Glu Ala Ile Ser Tyr Arg Lys Phe Thr Ser Ala Ser Asp Val  
 785 790 795 800

Trp Ser Phe Gly Ile Val Met Trp Glu Val Met Thr Tyr Gly Glu Arg  
 805 810 815

Pro Tyr Trp Glu Leu Ser Asn His Glu Val Met Lys Ala Ile Asn Asp  
 820 825 830

Gly Phe Arg Leu Pro Thr Pro Met Asp Cys Pro Ser Ala Ile Tyr Gln  
 835 840 845

Leu Met Met Gln Cys Trp Gln Gln Glu Arg Ala Arg Arg Pro Lys Phe  
 850 855 860

Ala Asp Ile Val Ser Ile Leu Asp Lys Leu Ile Arg Ala Pro Asp Ser  
 865 870 875 880

Leu Lys Thr Leu Ala Asp Phe Asp Pro Arg Val Ser Ile Arg Leu Pro  
 885 890 895

Ser Thr Ser Gly Ser Glu Gly Val Pro Phe Arg Thr Val Ser Glu Trp  
 900 905 910

Leu Glu Ser Ile Lys Met Gln Gln Tyr Thr Glu His Phe Met Ala Ala  
 915 920 925

Gly Tyr Thr Ala Ile Glu Lys Val Val Gln Met Thr Asn Asp Asp Ile  
 930 935 940

Lys Arg Ile Gly Val Arg Leu Pro Gly His Gln Lys Arg Ile Ala Tyr  
 945 950 955 960

Ser Leu Leu Gly Leu Lys Asp Gln Val Asn Thr Val Gly Ile Pro Ile  
 965 970 975

<210> 139  
 <211> 1055  
 <212> PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 139

Met Ala Leu Arg Arg Leu Gly Ala Ala Leu Leu Leu Leu Pro Leu Leu  
 1 5 10 15

Ala Ala Val Glu Glu Thr Leu Met Asp Ser Thr Thr Ala Thr Ala Glu  
 20 25 30

Leu Gly Trp Met Val His Pro Pro Ser Gly Trp Glu Glu Val Ser Gly  
 35 40 45

Tyr Asp Glu Asn Met Asn Thr Ile Arg Thr Tyr Gln Val Cys Asn Val  
 50 55 60

Phe Glu Ser Ser Gln Asn Asn Trp Leu Arg Thr Lys Phe Ile Arg Arg  
 65 70 75 80

Arg Gly Ala His Arg Ile His Val Glu Met Lys Phe Ser Val Arg Asp  
 85 90 95

Cys Ser Ser Ile Pro Ser Val Pro Gly Ser Cys Lys Glu Thr Phe Asn  
 100 105 110

Leu Tyr Tyr Tyr Glu Ala Asp Phe Asp Ser Ala Thr Lys Thr Phe Pro  
 115 120 125

Asn Trp Met Glu Asn Pro Trp Val Lys Val Asp Thr Ile Ala Ala Asp  
 130 135 140

Glu Ser Phe Ser Gln Val Asp Leu Gly Gly Arg Val Met Lys Ile Asn  
 145 150 155 160

Thr Glu Val Arg Ser Phe Gly Pro Val Ser Arg Ser Gly Phe Tyr Leu  
 165 170 175

Ala Phe Gln Asp Tyr Gly Gly Cys Met Ser Leu Ile Ala Val Arg Val  
 180 185 190

Phe Tyr Arg Lys Cys Pro Arg Ile Ile Gln Asn Gly Ala Ile Phe Gln  
 195 200 205

Glu Thr Leu Ser Gly Ala Glu Ser Thr Ser Leu Val Ala Ala Arg Gly

210		215		220
Ser Cys Ile Ala Asn Ala Glu Glu Val Asp Val Pro Ile Lys Leu Tyr				
225		230		240
Cys Asn Gly Asp Gly Glu Trp Leu Val Pro Ile Gly Arg Cys Met Cys				
	245		250	255
Lys Ala Gly Phe Glu Ala Val Glu Asn Gly Thr Val Cys Arg Gly Cys				
	260		265	270
Pro Ser Gly Thr Phe Lys Ala Asn Gln Gly Asp Glu Ala Cys Thr His				
	275		280	285
Cys Pro Ile Asn Ser Arg Thr Thr Ser Glu Gly Ala Thr Asn Cys Val				
	290		295	300
Cys Arg Asn Gly Tyr Tyr Arg Ala Asp Leu Asp Pro Leu Asp Met Pro				
305		310		320
Cys Thr Thr Ile Pro Ser Ala Pro Gln Ala Val Ile Ser Ser Val Asn				
	325		330	335
Glu Thr Ser Leu Met Leu Glu Trp Thr Pro Pro Arg Asp Ser Gly Gly				
	340		345	350
Arg Glu Asp Leu Val Tyr Asn Ile Ile Cys Lys Ser Cys Gly Ser Gly				
	355		360	365
Arg Gly Ala Cys Thr Arg Cys Gly Asp Asn Val Gln Tyr Ala Pro Arg				
	370		375	380
Gln Leu Gly Leu Thr Glu Pro Arg Ile Tyr Ile Ser Asp Leu Leu Ala				
385		390		400
His Thr Gln Tyr Thr Phe Glu Ile Gln Ala Val Asn Gly Val Thr Asp				
	405		410	415
Gln Ser Pro Phe Ser Pro Gln Phe Ala Ser Val Asn Ile Thr Thr Asn				
	420		425	430
Gln Ala Ala Pro Ser Ala Val Ser Ile Met His Gln Val Ser Arg Thr				
	435		440	445



Val Asp Ser Ile Thr Leu Ser Trp Ser Gln Pro Asp Gln Pro Asn Gly  
 450 455 460

Val Ile Leu Asp Tyr Glu Leu Gln Tyr Tyr Glu Lys Glu Leu Ser Glu  
 465 470 475 480

Tyr Asn Ala Thr Ala Ile Lys Ser Pro Thr Asn Thr Val Thr Val Gln  
 485 490 495

Gly Leu Lys Ala Gly Ala Ile Tyr Val Phe Gln Val Arg Ala Arg Thr  
 500 505 510

Val Ala Gly Tyr Gly Arg Tyr Ser Gly Lys Met Tyr Phe Gln Thr Met  
 515 520 525

Thr Glu Ala Glu Tyr Gln Thr Ser Ile Gln Glu Lys Leu Pro Leu Ile  
 530 535 540

Ile Gly Ser Ser Ala Ala Gly Leu Val Phe Leu Ile Ala Val Val Val  
 545 550 555 560

Ile Ala Ile Val Cys Asn Arg Arg Gly Phe Glu Arg Ala Asp Ser Glu  
 565 570 575

Tyr Thr Asp Lys Leu Gln His Tyr Thr Ser Gly His Met Thr Pro Gly  
 580 585 590

Met Lys Ile Tyr Ile Asp Pro Phe Thr Tyr Glu Asp Pro Asn Glu Ala  
 595 600 605

Val Arg Glu Phe Ala Lys Glu Ile Asp Ile Ser Cys Val Lys Ile Glu  
 610 615 620

Gln Val Ile Gly Ala Gly Glu Phe Gly Glu Val Cys Ser Gly His Leu  
 625 630 635 640

Lys Leu Pro Gly Lys Arg Glu Ile Phe Val Ala Ile Lys Thr Leu Lys  
 645 650 655

Ser Gly Tyr Thr Glu Lys Gln Arg Arg Asp Phe Leu Ser Glu Ala Ser  
 660 665 670

Ile Met Gly Gln Phe Asp His Pro Asn Val Ile His Leu Glu Gly Val  
 675 680 685

Val Thr Lys Ser Thr Pro Val Met Ile Ile Thr Glu Phe Met Glu Asn  
 690 695 700

Gly Ser Leu Asp Ser Phe Leu Arg Gln Asn Asp Gly Gln Phe Thr Val  
 705 710 715 720

Ile Gln Leu Val Gly Met Leu Arg Gly Ile Ala Ala Gly Met Lys Tyr  
 725 730 735

Leu Ala Asp Met Asn Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile  
 740 745 750

Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser  
 755 760 765

Arg Phe Leu Glu Asp Asp Thr Ser Asp Pro Thr Tyr Thr Ser Ala Leu  
 770 775 780

Gly Gly Lys Ile Pro Ile Arg Trp Thr Ala Pro Glu Ala Ile Gln Tyr  
 785 790 795 800

Arg Lys Phe Thr Ser Ala Ser Asp Val Trp Ser Tyr Gly Ile Val Met  
 805 810 815

Trp Glu Val Met Ser Tyr Gly Glu Arg Pro Tyr Trp Asp Met Thr Asn  
 820 825 830

Gln Asp Val Ile Asn Ala Ile Glu Gln Asp Tyr Arg Leu Pro Pro Pro  
 835 840 845

Met Asp Cys Pro Ser Ala Leu His Gln Leu Met Leu Asp Cys Trp Gln  
 850 855 860

Lys Asp Arg Asn His Arg Pro Lys Phe Gly Gln Ile Val Asn Thr Leu  
 865 870 875 880

Asp Lys Met Ile Arg Asn Pro Asn Ser Leu Lys Ala Met Ala Pro Leu  
 885 890 895

Ser Ser Gly Ile Asn Leu Pro Leu Leu Asp Arg Thr Ile Pro Asp Tyr  
 900 905 910

Thr Ser Phe Asn Thr Val Asp Glu Trp Leu Glu Ala Ile Lys Met Gly  
 915 920 925

Gln Tyr Lys Glu Ser Phe Ala Asn Ala Gly Phe Thr Ser Phe Asp Val  
 930 935 940

Val Ser Gln Met Met Met Glu Asp Ile Leu Arg Val Gly Val Thr Leu  
 945 950 955 960

Ala Gly His Gln Lys Lys Ile Leu Asn Ser Ile Gln Val Met Arg Ala  
 965 970 975

Gln Met Asn Gln Ile Gln Ser Val Glu Gly Gln Pro Leu Ala Arg Arg  
 980 985 990

Pro Arg Ala Thr Gly Arg Thr Lys Arg Cys Gln Pro Arg Asp Val Thr  
 995 1000 1005

Lys Lys Thr Cys Asn Ser Asn Asp Gly Lys Lys Lys Gly Met Gly  
 1010 1015 1020

Lys Lys Lys Thr Asp Pro Gly Arg Gly Arg Glu Ile Gln Gly Ile  
 1025 1030 1035

Phe Phe Lys Glu Asp Ser His Lys Glu Ser Asn Asp Cys Ser Cys  
 1040 1045 1050

Gly Gly  
 1055

<210> 140  
 <211> 178  
 <212> PRT  
 <213> Homo sapiens

<400> 140

Met Ser Gly Gly Lys Tyr Val Asp Ser Glu Gly His Leu Tyr Thr Val  
 1 5 10 15

Pro Ile Arg Glu Gln Gly Asn Ile Tyr Lys Pro Asn Asn Lys Ala Met  
 20 25 30

Ala Asp Glu Leu Ser Glu Lys Gln Val Tyr Asp Ala His Thr Lys Glu  
 35 40 45

Ile Asp Leu Val Asn Arg Asp Pro Lys His Leu Asn Asp Asp Val Val  
 50 55 60

Lys Ile Asp Phe Glu Asp Val Ile Ala Glu Pro Glu Gly Thr His Ser  
 65 70 75 80

Phe Asp Gly Ile Trp Lys Ala Ser Phe Thr Thr Phe Thr Val Thr Lys  
 85 90 95

Tyr Trp Phe Tyr Arg Leu Leu Ser Ala Leu Phe Gly Ile Pro Met Ala  
 100 105 110

Leu Ile Trp Gly Ile Tyr Phe Ala Ile Leu Ser Phe Leu His Ile Trp  
 115 120 125

Ala Val Val Pro Cys Ile Lys Ser Phe Leu Ile Glu Ile Gln Cys Ile  
 130 135 140

Ser Arg Val Tyr Ser Ile Tyr Val His Thr Val Cys Asp Pro Leu Phe  
 145 150 155 160

Glu Ala Val Gly Lys Ile Phe Ser Asn Val Arg Ile Asn Leu Gln Lys  
 165 170 175

Glu Ile

<210> 141  
 <211> 162  
 <212> PRT  
 <213> Homo sapiens

<400> 141

Met Gly Leu Glu Thr Glu Lys Ala Asp Val Gln Leu Phe Met Asp Asp  
 1 5 10 15

Asp Ser Tyr Ser His His Ser Gly Leu Glu Tyr Ala Asp Pro Glu Lys  
 20 25 30

Phe Ala Asp Ser Asp Gln Asp Arg Asp Pro His Arg Leu Asn Ser His  
 35 40 45

Leu Lys Leu Gly Phe Glu Asp Val Ile Ala Glu Pro Val Thr Thr His  
 50 55 60

Ser Phe Asp Lys Val Trp Ile Cys Ser His Ala Leu Phe Glu Ile Ser  
 65 70 75 80

Lys Tyr Val Met Tyr Lys Phe Leu Thr Val Phe Leu Ala Ile Pro Leu  
 85 90 95

Ala Phe Ile Ala Gly Ile Leu Phe Ala Thr Leu Ser Cys Leu His Ile  
 100 105 110

Trp Ile Leu Met Pro Phe Val Lys Thr Cys Leu Met Val Leu Pro Ser  
 115 120 125

Val Gln Thr Ile Trp Lys Ser Val Thr Asp Val Ile Ile Ala Pro Leu  
 130 135 140

Cys Thr Ser Val Gly Arg Cys Phe Ser Ser Val Ser Leu Gln Leu Ser  
 145 150 155 160

Gln Asp

<210> 142  
 <211> 346  
 <212> PRT  
 <213> Homo sapiens

<400> 142

Met Ala Met Val Ser Glu Phe Leu Lys Gln Ala Trp Phe Ile Glu Asn  
 1 5 10 15

Glu Glu Gln Glu Tyr Val Gln Thr Val Lys Ser Ser Lys Gly Gly Pro  
 20 25 30

Gly Ser Ala Val Ser Pro Tyr Pro Thr Phe Asn Pro Ser Ser Asp Val  
 35 40 45

Ala Ala Leu His Lys Ala Ile Met Val Lys Gly Val Asp Glu Ala Thr  
 50 55 60

Ile Ile Asp Ile Leu Thr Lys Arg Asn Asn Ala Gln Arg Gln Gln Ile  
 65 70 75 80

Lys Ala Ala Tyr Leu Gln Glu Thr Gly Lys Pro Leu Asp Glu Thr Leu  
 85 90 95

Lys Lys Ala Leu Thr Gly His Leu Glu Glu Val Val Leu Ala Leu Leu  
 100 105 110

Lys Thr Pro Ala Gln Phe Asp Ala Asp Glu Leu Arg Ala Ala Met Lys  
 115 120 125

Gly Leu Gly Thr Asp Glu Asp Thr Leu Ile Glu Ile Leu Ala Ser Arg  
 130 135 140

Thr Asn Lys Glu Ile Arg Asp Ile Asn Arg Val Tyr Arg Glu Glu Leu  
 145 150 155 160

Lys Arg Asp Leu Ala Lys Asp Ile Thr Ser Asp Thr Ser Gly Asp Phe  
 165 170 175

Arg Asn Ala Leu Leu Ser Leu Ala Lys Gly Asp Arg Ser Glu Asp Phe  
 180 185 190

Gly Val Asn Glu Asp Leu Ala Asp Ser Asp Ala Arg Ala Leu Tyr Glu  
 195 200 205

Ala Gly Glu Arg Arg Lys Gly Thr Asp Val Asn Val Phe Asn Thr Ile  
 210 215 220

Leu Thr Thr Arg Ser Tyr Pro Gln Leu Arg Arg Val Phe Gln Lys Tyr  
 225 230 235 240

Thr Lys Tyr Ser Lys His Asp Met Asn Lys Val Leu Asp Leu Glu Leu  
 245 250 255

Lys Gly Asp Ile Glu Lys Cys Leu Thr Ala Ile Val Lys Cys Ala Thr  
 260 265 270

Ser Lys Pro Ala Phe Phe Ala Glu Lys Leu His Gln Ala Met Lys Gly  
 275 280 285

Val Gly Thr Arg His Lys Ala Leu Ile Arg Ile Met Val Ser Arg Ser  
 290 295 300

Glu Ile Asp Met Asn Asp Ile Lys Ala Phe Tyr Gln Lys Met Tyr Gly  
 305 310 315 320

Ile Ser Leu Cys Gln Ala Ile Leu Asp Glu Thr Lys Gly Asp Tyr Glu  
 325 330 335

Lys Ile Leu Val Ala Leu Cys Gly Gly Asn  
 340 345

<210> 143  
 <211> 339  
 <212> PRT  
 <213> Homo sapiens

<400> 143

Met Ser Thr Val His Glu Ile Leu Cys Lys Leu Ser Leu Glu Gly Asp  
 1 5 10 15

His Ser Thr Pro Pro Ser Ala Tyr Gly Ser Val Lys Ala Tyr Thr Asn  
 20 25 30

Phe Asp Ala Glu Arg Asp Ala Leu Asn Ile Glu Thr Ala Ile Lys Thr  
 35 40 45

Lys Gly Val Asp Glu Val Thr Ile Val Asn Ile Leu Thr Asn Arg Ser  
 50 55 60

Asn Ala Gln Arg Gln Asp Ile Ala Phe Ala Tyr Gln Arg Arg Thr Lys  
 65 70 75 80

Lys Glu Leu Ala Ser Ala Leu Lys Ser Ala Leu Ser Gly His Leu Glu  
 85 90 95

Thr Val Ile Leu Gly Leu Leu Lys Thr Pro Ala Gln Tyr Asp Ala Ser  
 100 105 110

Glu Leu Lys Ala Ser Met Lys Gly Leu Gly Thr Asp Glu Asp Ser Leu  
 115 120 125

Ile Glu Ile Ile Cys Ser Arg Thr Asn Gln Glu Leu Gln Glu Ile Asn

130

135

140

Arg Val Tyr Lys Glu Met Tyr Lys Thr Asp Leu Glu Lys Asp Ile Ile  
 145 150 155 160

Ser Asp Thr Ser Gly Asp Phe Arg Lys Leu Met Val Ala Leu Ala Lys  
 165 170 175

Gly Arg Arg Ala Glu Asp Gly Ser Val Ile Asp Tyr Glu Leu Ile Asp  
 180 185 190

Gln Asp Ala Arg Asp Leu Tyr Asp Ala Gly Val Lys Arg Lys Gly Thr  
 195 200 205

Asp Val Pro Lys Trp Ile Ser Ile Met Thr Glu Arg Ser Val Pro His  
 210 215 220

Leu Gln Lys Val Phe Asp Arg Tyr Lys Ser Tyr Ser Pro Tyr Asp Met  
 225 230 235 240

Leu Glu Ser Ile Arg Lys Glu Val Lys Gly Asp Leu Glu Asn Ala Phe  
 245 250 255

Leu Asn Leu Val Gln Cys Ile Gln Asn Lys Pro Leu Tyr Phe Ala Asp  
 260 265 270

Arg Leu Tyr Asp Ser Met Lys Gly Lys Gly Thr Arg Asp Lys Val Leu  
 275 280 285

Ile Arg Ile Met Val Ser Arg Ser Glu Val Asp Met Leu Lys Ile Arg  
 290 295 300

Ser Glu Phe Lys Arg Lys Tyr Gly Lys Ser Leu Tyr Tyr Tyr Ile Gln  
 305 310 315 320

Gln Asp Thr Lys Gly Asp Tyr Gln Lys Ala Leu Leu Tyr Leu Cys Gly  
 325 330 335

Gly Asp Asp

<210> 144

<211> 372



&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 144

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Met Ala Thr Ser Pro Gln Lys Ser Pro Ser Val Pro Lys Ser Pro Thr
1           5           10           15

Pro Lys Ser Pro Pro Ser Arg Lys Lys Asp Asp Ser Phe Leu Gly Lys
          20           25           30

Leu Gly Gly Thr Leu Ala Arg Arg Lys Lys Ala Lys Glu Val Ser Glu
      35           40           45

Leu Gln Glu Glu Gly Met Asn Ala Ile Asn Leu Pro Leu Ser Pro Ile
      50           55           60

Pro Phe Glu Leu Asp Pro Glu Asp Thr Met Leu Glu Glu Asn Glu Val
65           70           75           80

Arg Thr Met Val Asp Pro Asn Ser Arg Ser Asp Pro Lys Leu Gln Glu
          85           90           95

Leu Met Lys Val Leu Ile Asp Trp Ile Asn Asp Val Leu Val Gly Glu
          100          105          110

Arg Ile Ile Val Lys Asp Leu Ala Glu Asp Leu Tyr Asp Gly Gln Val
      115           120           125

Leu Gln Lys Leu Phe Glu Lys Leu Glu Ser Glu Lys Leu Asn Val Ala
      130           135           140

Glu Val Thr Gln Ser Glu Ile Ala Gln Lys Gln Lys Leu Gln Thr Val
145           150           155           160

Leu Glu Lys Ile Asn Glu Thr Leu Lys Leu Pro Pro Arg Ser Ile Lys
          165           170           175

Trp Asn Val Asp Ser Val His Ala Lys Ser Leu Val Ala Ile Leu His
          180           185           190

Leu Leu Val Ala Leu Ser Gln Tyr Phe Arg Ala Pro Ile Arg Leu Pro
      195           200           205

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Asp His Val Ser Ile Gln Val Val Val Val Gln Lys Arg Glu Gly Ile  
 210 215 220

Leu Gln Ser Arg Gln Ile Gln Glu Glu Ile Thr Gly Asn Thr Glu Ala  
 225 230 235 240

Leu Ser Gly Arg His Glu Arg Asp Ala Phe Asp Thr Leu Phe Asp His  
 245 250 255

Ala Pro Asp Lys Leu Asn Val Val Lys Lys Thr Leu Ile Thr Phe Val  
 260 265 270

Asn Lys His Leu Asn Lys Leu Asn Leu Glu Val Thr Glu Leu Glu Thr  
 275 280 285

Gln Phe Ala Asp Gly Val Tyr Leu Val Leu Leu Met Gly Leu Leu Glu  
 290 295 300

Gly Tyr Phe Val Pro Leu His Ser Phe Phe Leu Thr Pro Asp Ser Phe  
 305 310 315 320

Glu Gln Lys Val Leu Asn Val Ser Phe Ala Phe Glu Leu Met Gln Asp  
 325 330 335

Gly Gly Leu Glu Lys Pro Lys Pro Arg Pro Glu Asp Ile Val Asn Cys  
 340 345 350

Asp Leu Lys Ser Thr Leu Arg Val Leu Tyr Asn Leu Phe Thr Lys Tyr  
 355 360 365

Arg Asn Val Glu  
 370

<210> 145  
 <211> 397  
 <212> PRT  
 <213> Homo sapiens

<400> 145

Met Arg Ser Pro Ser Ala Ala Trp Leu Leu Gly Ala Ala Ile Leu Leu  
 1 5 10 15

Ala Ala Ser Leu Ser Cys Ser Gly Thr Ile Gln Gly Thr Ser Arg Ser  
 20 25 30

Ser Lys Gly Arg Ser Leu Ile Gly Lys Val Asp Gly Thr Ser His Val  
 35 40 45

Thr Gly Lys Gly Val Thr Val Glu Thr Val Phe Ser Val Asp Glu Phe  
 50 55 60

Ser Ala Ser Val Leu Thr Gly Lys Leu Thr Thr Val Phe Leu Pro Ile  
 65 70 75 80

Val Tyr Thr Ile Val Phe Val Val Gly Leu Pro Ser Asn Gly Met Ala  
 85 90 95

Leu Trp Val Phe Leu Phe Arg Thr Lys Lys Lys His Pro Ala Val Ile  
 100 105 110

Tyr Met Ala Asn Leu Ala Leu Ala Asp Leu Leu Ser Val Ile Trp Phe  
 115 120 125

Pro Leu Lys Ile Ala Tyr His Ile His Gly Asn Asn Trp Ile Tyr Gly  
 130 135 140

Glu Ala Leu Cys Asn Val Leu Ile Gly Phe Phe Tyr Gly Asn Met Tyr  
 145 150 155 160

Cys Ser Ile Leu Phe Met Thr Cys Leu Ser Val Gln Arg Tyr Trp Val  
 165 170 175

Ile Val Asn Pro Met Gly His Ser Arg Lys Lys Ala Asn Ile Ala Ile  
 180 185 190

Gly Ile Ser Leu Ala Ile Trp Leu Leu Ile Leu Leu Val Thr Ile Pro  
 195 200 205

Leu Tyr Val Val Lys Gln Thr Ile Phe Ile Pro Ala Leu Asn Ile Thr  
 210 215 220

Thr Cys His Asp Val Leu Pro Glu Gln Leu Leu Val Gly Asp Met Phe  
 225 230 235 240

Asn Tyr Phe Leu Ser Leu Ala Ile Gly Val Phe Leu Phe Pro Ala Phe  
 245 250 255

Leu Thr Ala Ser Ala Tyr Val Leu Met Ile Arg Met Leu Arg Ser Ser  
 260 265 270

Ala Met Asp Glu Asn Ser Glu Lys Lys Arg Lys Arg Ala Ile Lys Leu  
 275 280 285

Ile Val Thr Val Leu Ala Met Tyr Leu Ile Cys Phe Thr Pro Ser Asn  
 290 295 300

Leu Leu Leu Val Val His Tyr Phe Leu Ile Lys Ser Gln Gly Gln Ser  
 305 310 315 320

His Val Tyr Ala Leu Tyr Ile Val Ala Leu Cys Leu Ser Thr Leu Asn  
 325 330 335

Ser Cys Ile Asp Pro Phe Val Tyr Tyr Phe Val Ser His Asp Phe Arg  
 340 345 350

Asp His Ala Lys Asn Ala Leu Leu Cys Arg Ser Val Arg Thr Val Lys  
 355 360 365

Gln Met Gln Val Ser Leu Thr Ser Lys Lys His Ser Arg Lys Ser Ser  
 370 375 380

Ser Tyr Ser Ser Ser Ser Thr Thr Val Lys Thr Ser Tyr  
 385 390 395

<210> 146  
 <211> 295  
 <212> PRT  
 <213> Homo sapiens

<400> 146

Met Glu Thr Pro Ala Trp Pro Arg Val Pro Arg Pro Glu Thr Ala Val  
 1 5 10 15

Ala Arg Thr Leu Leu Leu Gly Trp Val Phe Ala Gln Val Ala Gly Ala  
 20 25 30

Ser Gly Thr Thr Asn Thr Val Ala Ala Tyr Asn Leu Thr Trp Lys Ser  
 35 40 45

Thr Asn Phe Lys Thr Ile Leu Glu Trp Glu Pro Lys Pro Val Asn Gln

50		55		60
Val Tyr Thr Val Gln Ile Ser Thr Lys Ser Gly Asp Trp Lys Ser Lys				
65		70		75 80
Cys Phe Tyr Thr Thr Asp Thr Glu Cys Asp Leu Thr Asp Glu Ile Val				
		85		90 95
Lys Asp Val Lys Gln Thr Tyr Leu Ala Arg Val Phe Ser Tyr Pro Ala				
		100		105 110
Gly Asn Val Glu Ser Thr Gly Ser Ala Gly Glu Pro Leu Tyr Glu Asn				
		115		120 125
Ser Pro Glu Phe Thr Pro Tyr Leu Glu Thr Asn Leu Gly Gln Pro Thr				
		130		135 140
Ile Gln Ser Phe Glu Gln Val Gly Thr Lys Val Asn Val Thr Val Glu				
145		150		155 160
Asp Glu Arg Thr Leu Val Arg Arg Asn Asn Thr Phe Leu Ser Leu Arg				
		165		170 175
Asp Val Phe Gly Lys Asp Leu Ile Tyr Thr Leu Tyr Tyr Trp Lys Ser				
		180		185 190
Ser Ser Ser Gly Lys Lys Thr Ala Lys Thr Asn Thr Asn Glu Phe Leu				
		195		200 205
Ile Asp Val Asp Lys Gly Glu Asn Tyr Cys Phe Ser Val Gln Ala Val				
210		215		220
Ile Pro Ser Arg Thr Val Asn Arg Lys Ser Thr Asp Ser Pro Val Glu				
225		230		235 240
Cys Met Gly Gln Glu Lys Gly Glu Phe Arg Glu Ile Phe Tyr Ile Ile				
		245		250 255
Gly Ala Val Val Phe Val Val Ile Ile Leu Val Ile Ile Leu Ala Ile				
		260		265 270
Ser Leu His Lys Cys Arg Lys Ala Gly Val Gly Gln Ser Trp Lys Glu				
		275		280 285

Asn Ser Pro Leu Asn Val Ser  
290 295

<210> 147  
<211> 491  
<212> PRT  
<213> Homo sapiens

<400> 147

Met Ala Gln Ser Gly Gly Glu Ala Arg Pro Gly Pro Lys Thr Ala Val  
1 5 10 15

Gln Ile Arg Val Ala Ile Gln Glu Ala Glu Asp Val Asp Glu Leu Glu  
20 25 30

Asp Glu Glu Glu Gly Ala Glu Thr Arg Gly Ala Gly Asp Pro Ala Arg  
35 40 45

Tyr Leu Ser Pro Gly Trp Gly Ser Ala Ser Glu Glu Glu Pro Ser Arg  
50 55 60

Gly His Ser Gly Thr Thr Ala Ser Gly Gly Glu Asn Glu Arg Glu Asp  
65 70 75 80

Leu Glu Gln Glu Trp Lys Pro Pro Asp Glu Glu Leu Ile Lys Lys Leu  
85 90 95

Val Asp Gln Ile Glu Phe Cys Phe Ser Asp Glu Asn Leu Glu Lys Asp  
100 105 110

Ala Phe Leu Leu Lys His Val Arg Arg Asn Lys Leu Gly Tyr Val Ser  
115 120 125

Val Lys Leu Leu Thr Ser Phe Lys Lys Val Lys His Leu Thr Arg Asp  
130 135 140

Trp Arg Thr Thr Ala His Ala Leu Lys Tyr Ser Val Val Leu Glu Leu  
145 150 155 160

Asn Glu Asp His Arg Lys Val Arg Arg Thr Thr Pro Val Pro Leu Phe  
165 170 175

Pro Asn Glu Asn Leu Pro Ser Lys Met Leu Leu Val Tyr Asp Leu Tyr  
 180 185 190

Leu Ser Pro Lys Leu Trp Ala Leu Ala Thr Pro Gln Lys Asn Gly Arg  
 195 200 205

Val Gln Glu Lys Val Met Glu His Leu Leu Lys Leu Phe Gly Thr Phe  
 210 215 220

Gly Val Ile Ser Ser Val Arg Ile Leu Lys Pro Gly Arg Glu Leu Pro  
 225 230 235 240

Pro Asp Ile Arg Arg Ile Ser Ser Arg Tyr Ser Gln Val Gly Thr Gln  
 245 250 255

Glu Cys Ala Ile Val Glu Phe Glu Glu Val Glu Ala Ala Ile Lys Ala  
 260 265 270

His Glu Phe Met Ile Thr Glu Ser Gln Gly Lys Glu Asn Met Lys Ala  
 275 280 285

Val Leu Ile Gly Met Lys Pro Pro Lys Lys Lys Pro Ala Lys Asp Lys  
 290 295 300

Asn His Asp Glu Glu Pro Thr Ala Ser Ile His Leu Asn Lys Ser Leu  
 305 310 315 320

Asn Lys Arg Val Glu Glu Leu Gln Tyr Met Gly Asp Glu Ser Ser Ala  
 325 330 335

Asn Ser Ser Ser Asp Pro Glu Ser Asn Pro Thr Ser Pro Met Ala Gly  
 340 345 350

Arg Arg His Ala Ala Thr Asn Lys Leu Ser Pro Ser Gly His Gln Asn  
 355 360 365

Leu Phe Leu Ser Pro Asn Ala Ser Pro Cys Thr Ser Pro Trp Ser Ser  
 370 375 380

Pro Leu Ala Gln Arg Lys Gly Val Ser Arg Lys Ser Pro Leu Ala Glu  
 385 390 395 400

Glu Gly Arg Leu Asn Cys Ser Thr Ser Pro Glu Ile Phe Arg Lys Cys

405                                      410                                      415  
 Met Asp Tyr Ser Ser Asp Ser Ser Val Thr Pro Ser Gly Ser Pro Trp  
    420                                      425                                      430  
 Val Arg Arg Arg Arg Gln Ala Glu Met Gly Thr Gln Glu Lys Ser Pro  
    435                                      440                                      445  
 Gly Thr Ser Pro Leu Leu Ser Arg Lys Met Gln Thr Ala Asp Gly Leu  
    450                                      455                                      460  
 Pro Val Gly Val Leu Arg Leu Pro Arg Gly Pro Asp Asn Thr Arg Gly  
    465                                      470                                      475                                      480  
 Phe His Gly His Glu Arg Ser Arg Ala Cys Val  
    485                                      490  
  
 <210> 148  
 <211> 374  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 148  
 Met Arg Pro Gly Thr Ala Leu Gln Ala Val Leu Leu Ala Val Leu Leu  
 1                                      5                                      10                                      15  
  
 Val Gly Leu Arg Ala Ala Thr Gly Arg Leu Leu Ser Gly Gln Pro Val  
    20                                      25                                      30  
  
 Cys Arg Gly Gly Thr Gln Arg Pro Cys Tyr Lys Val Ile Tyr Phe His  
    35                                      40                                      45  
  
 Asp Thr Ser Arg Arg Leu Asn Phe Glu Glu Ala Lys Glu Ala Cys Arg  
    50                                      55                                      60  
  
 Arg Asp Gly Gly Gln Leu Val Ser Ile Glu Ser Glu Asp Glu Gln Lys  
 65                                      70                                      75                                      80  
  
 Leu Ile Glu Lys Phe Ile Glu Asn Leu Leu Pro Ser Asp Gly Asp Phe  
    85                                      90                                      95  
  
 Trp Ile Gly Leu Arg Arg Arg Glu Glu Lys Gln Ser Asn Ser Thr Ala  
    100                                      105                                      110



Cys Gln Asp Leu Tyr Ala Trp Thr Asp Gly Ser Ile Ser Gln Phe Arg  
 115 120 125

Asn Trp Tyr Val Asp Glu Pro Ser Cys Gly Ser Glu Val Cys Val Val  
 130 135 140

Met Tyr His Gln Pro Ser Ala Pro Ala Gly Ile Gly Gly Pro Tyr Met  
 145 150 155 160

Phe Gln Trp Asn Asp Asp Arg Cys Asn Met Lys Asn Asn Phe Ile Cys  
 165 170 175

Lys Tyr Ser Asp Glu Lys Pro Ala Val Pro Ser Arg Glu Ala Glu Gly  
 180 185 190

Glu Glu Thr Glu Leu Thr Thr Pro Val Leu Pro Glu Glu Thr Gln Glu  
 195 200 205

Glu Asp Ala Lys Lys Thr Phe Lys Glu Ser Arg Glu Ala Ala Leu Asn  
 210 215 220

Leu Ala Tyr Ile Leu Ile Pro Ser Ile Pro Leu Leu Leu Leu Leu Val  
 225 230 235 240

Val Thr Thr Val Val Cys Trp Val Trp Ile Cys Arg Lys Arg Lys Arg  
 245 250 255

Glu Gln Pro Asp Pro Ser Thr Lys Lys Gln His Thr Ile Trp Pro Ser  
 260 265 270

Pro His Gln Gly Asn Ser Pro Asp Leu Glu Val Tyr Asn Val Ile Arg  
 275 280 285

Lys Gln Ser Glu Ala Asp Leu Ala Glu Thr Arg Pro Asp Leu Lys Asn  
 290 295 300

Ile Ser Phe Arg Val Cys Ser Gly Glu Ala Thr Pro Asp Asp Met Ser  
 305 310 315 320

Cys Asp Tyr Asp Asn Met Ala Val Asn Pro Ser Glu Ser Gly Phe Val  
 325 330 335

Thr Leu Val Ser Val Glu Ser Gly Phe Val Thr Asn Asp Ile Tyr Glu  
                   340                  345                  350

Phe Ser Pro Asp Gln Met Gly Arg Ser Lys Glu Ser Gly Trp Val Glu  
           355                  360                  365

Asn Glu Ile Tyr Gly Tyr  
       370

<210> 149  
 <211> 276  
 <212> PRT  
 <213> Homo sapiens

<400> 149

Met Ala Leu Leu Asp Val Cys Gly Ala Pro Arg Gly Gln Arg Pro Glu  
   1                  5                  10                  15

Ser Ala Leu Pro Val Ala Gly Ser Gly Arg Arg Ser Asp Pro Gly His  
           20                  25                  30

Tyr Ser Phe Ser Met Arg Ser Pro Glu Leu Ala Leu Pro Arg Gly Met  
       35                  40                  45

Lys Pro Thr Glu Phe Phe Gln Ser Leu Gly Gly Asp Gly Glu Arg Asn  
       50                  55                  60

Val Gln Ile Glu Met Ala His Gly Thr Thr Thr Leu Ala Phe Lys Phe  
   65                  70                  75                  80

Gln His Gly Val Ile Ala Ala Val Asp Ser Arg Ala Ser Ala Gly Ser  
           85                  90                  95

Tyr Ile Ser Ala Leu Arg Val Asn Lys Val Ile Glu Ile Asn Pro Tyr  
           100                  105                  110

Leu Leu Gly Thr Met Ser Gly Cys Ala Ala Asp Cys Gln Tyr Trp Glu  
       115                  120                  125

Arg Leu Leu Ala Lys Glu Cys Arg Leu Tyr Tyr Leu Arg Asn Gly Glu  
       130                  135                  140

Arg Ile Ser Val Ser Ala Ala Ser Lys Leu Leu Ser Asn Met Met Cys  
       145                  150                  155                  160

Gln Tyr Arg Gly Met Gly Leu Ser Met Gly Ser Met Ile Cys Gly Trp  
                   165                  170                  175

Asp Lys Lys Gly Pro Gly Leu Tyr Tyr Val Asp Glu His Gly Thr Arg  
                   180                  185                  190

Leu Ser Gly Asn Met Phe Ser Thr Gly Ser Gly Asn Thr Tyr Ala Tyr  
                   195                  200                  205

Gly Val Met Asp Ser Gly Tyr Arg Pro Asn Leu Ser Pro Glu Glu Ala  
                   210                  215                  220

Tyr Asp Leu Gly Arg Arg Ala Ile Ala Tyr Ala Thr His Arg Asp Ser  
                   225                  230                  235                  240

Tyr Ser Gly Gly Val Val Asn Met Tyr His Met Lys Glu Asp Gly Trp  
                   245                  250                  255

Val Lys Val Glu Ser Thr Asp Val Ser Asp Leu Leu His Gln Tyr Arg  
                   260                  265                  270

Glu Ala Asn Gln  
                   275

<210> 150  
 <211> 219  
 <212> PRT  
 <213> Homo sapiens

<400> 150

Met Leu Arg Ala Gly Ala Pro Thr Gly Asp Leu Pro Arg Ala Gly Glu  
   1                  5                  10                  15

Val His Thr Gly Thr Thr Ile Met Ala Val Glu Phe Asp Gly Gly Val  
                   20                  25                  30

Val Met Gly Ser Asp Ser Arg Val Ser Ala Gly Glu Ala Val Val Asn  
                   35                  40                  45

Arg Val Phe Asp Lys Leu Ser Pro Leu His Glu Arg Ile Tyr Cys Ala  
                   50                  55                  60

Leu Ser Gly Ser Ala Ala Asp Ala Gln Ala Val Ala Asp Met Ala Ala  
65 70 75 80

Tyr Gln Leu Glu Leu His Gly Ile Glu Leu Glu Glu Pro Pro Leu Val  
85 90 95

Leu Ala Ala Ala Asn Val Val Arg Asn Ile Ser Tyr Lys Tyr Arg Glu  
100 105 110

Asp Leu Ser Ala His Leu Met Val Ala Gly Trp Asp Gln Arg Glu Gly  
115 120 125

Gly Gln Val Tyr Gly Thr Leu Gly Gly Met Leu Thr Arg Gln Pro Phe  
130 135 140

Ala Ile Gly Gly Ser Gly Ser Thr Phe Ile Tyr Gly Tyr Val Asp Ala  
145 150 155 160

Ala Tyr Lys Pro Gly Met Ser Pro Glu Glu Cys Arg Arg Phe Thr Thr  
165 170 175

Asp Ala Ile Ala Leu Ala Met Ser Arg Asp Gly Ser Ser Gly Gly Val  
180 185 190

Ile Tyr Leu Val Thr Ile Thr Ala Ala Gly Val Asp His Arg Val Ile  
195 200 205

Leu Gly Asn Glu Leu Pro Lys Phe Tyr Asp Glu  
210 215

<210> 151  
<211> 253  
<212> PRT  
<213> Homo sapiens

<400> 151

Met Ala Asn Leu Gly Cys Trp Met Leu Val Leu Phe Val Ala Thr Trp  
1 5 10 15

Ser Asp Leu Gly Leu Cys Lys Lys Arg Pro Lys Pro Gly Gly Trp Asn  
20 25 30

Thr Gly Gly Ser Arg Tyr Pro Gly Gln Gly Ser Pro Gly Gly Asn Arg  
35 40 45

Tyr Pro Pro Gln Gly Gly Gly Gly Trp Gly Gln Pro His Gly Gly Gly  
 50 55 60

Trp Gly Gln Pro His Gly Gly Gly Trp Gly Gln Pro His Gly Gly Gly  
 65 70 75 80

Trp Gly Gln Pro His Gly Gly Gly Trp Gly Gln Gly Gly Gly Thr His  
 85 90 95

Ser Gln Trp Asn Lys Pro Ser Lys Pro Lys Thr Asn Met Lys His Met  
 100 105 110

Ala Gly Ala Ala Ala Ala Gly Ala Val Val Gly Gly Leu Gly Gly Tyr  
 115 120 125

Met Leu Gly Ser Ala Met Ser Arg Pro Ile Ile His Phe Gly Ser Asp  
 130 135 140

Tyr Glu Asp Arg Tyr Tyr Arg Glu Asn Met His Arg Tyr Pro Asn Gln  
 145 150 155 160

Val Tyr Tyr Arg Pro Met Asp Glu Tyr Ser Asn Gln Asn Asn Phe Val  
 165 170 175

His Asp Cys Val Asn Ile Thr Ile Lys Gln His Thr Val Thr Thr Thr  
 180 185 190

Thr Lys Gly Glu Asn Phe Thr Glu Thr Asp Val Lys Met Met Glu Arg  
 195 200 205

Val Val Glu Gln Met Cys Ile Thr Gln Tyr Glu Arg Glu Ser Gln Ala  
 210 215 220

Tyr Tyr Gln Arg Gly Ser Ser Met Val Leu Phe Ser Ser Pro Pro Val  
 225 230 235 240

Ile Leu Leu Ile Ser Phe Leu Ile Phe Leu Ile Val Gly  
 245 250

<210> 152

<211> 323

<212> PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 152

Met Asp Ser Lys Gln Gln Cys Val Lys Leu Asn Asp Gly His Phe Met  
 1 5 10 15

Pro Val Leu Gly Phe Gly Thr Tyr Ala Pro Pro Glu Val Pro Arg Ser  
 20 25 30

Lys Ala Leu Glu Val Ser Lys Leu Ala Ile Glu Ala Gly Phe Arg His  
 35 40 45

Ile Asp Ser Ala His Leu Tyr Asn Asn Glu Glu Gln Val Gly Leu Ala  
 50 55 60

Ile Arg Ser Lys Ile Ala Asp Gly Ser Val Lys Arg Glu Asp Ile Phe  
 65 70 75 80

Tyr Thr Ser Lys Leu Trp Ser Thr Ser His Arg Pro Glu Leu Val Arg  
 85 90 95

Pro Ala Leu Glu Asn Ser Leu Lys Lys Ala Gln Leu Asp Tyr Val Asp  
 100 105 110

Leu Tyr Leu Ile His Ser Pro Met Ser Leu Lys Pro Gly Glu Glu Leu  
 115 120 125

Ser Pro Thr Asp Glu Asn Gly Lys Val Ile Phe Asp Ile Val Asp Leu  
 130 135 140

Cys Thr Thr Trp Glu Ala Met Glu Lys Cys Lys Asp Ala Gly Leu Ala  
 145 150 155 160

Lys Ser Ile Gly Val Ser Asn Phe Asn Arg Arg Gln Leu Glu Met Ile  
 165 170 175

Leu Asn Lys Pro Gly Leu Lys Tyr Lys Pro Val Cys Asn Gln Val Glu  
 180 185 190

Cys His Pro Tyr Phe Asn Arg Ser Lys Leu Leu Asp Phe Cys Lys Ser  
 195 200 205

Lys Asp Ile Val Leu Val Ala Tyr Ser Ala Leu Gly Ser Gln Arg Asp

210

215

220

Lys Arg Trp Val Asp Pro Asn Ser Pro Val Leu Leu Glu Asp Pro Val  
 225 230 235 240

Leu Cys Ala Leu Ala Lys Lys His Lys Arg Thr Pro Ala Leu Ile Ala  
 245 250 255

Leu Arg Tyr Gln Leu Gln Arg Gly Val Val Val Leu Ala Arg Ser Tyr  
 260 265 270

Asn Glu Gln Arg Ile Arg Gln Asn Val Gln Val Phe Glu Phe Gln Leu  
 275 280 285

Thr Ala Glu Asp Met Lys Ala Ile Asp Gly Leu Asp Arg Asn Leu His  
 290 295 300

Tyr Phe Asn Ser Asp Ser Phe Ala Ser His Pro Asn Tyr Pro Tyr Ser  
 305 310 315 320

Asp Glu Tyr

<210> 153  
 <211> 784  
 <212> PRT  
 <213> Homo sapiens

<400> 153

Met Glu Gly Asp Gly Gly Thr Pro Trp Ala Leu Ala Leu Leu Arg Thr  
 1 5 10 15

Phe Asp Ala Gly Glu Phe Thr Gly Trp Glu Lys Val Gly Ser Gly Gly  
 20 25 30

Phe Gly Gln Val Tyr Lys Val Arg His Val His Trp Lys Thr Trp Leu  
 35 40 45

Ala Ile Lys Cys Ser Pro Ser Leu His Val Asp Asp Arg Glu Arg Met  
 50 55 60

Glu Leu Leu Glu Glu Ala Lys Lys Met Glu Met Ala Lys Phe Arg Tyr  
 65 70 75 80

Ile Leu Pro Val Tyr Gly Ile Cys Arg Glu Pro Val Gly Leu Val Met  
85 90 95

Glu Tyr Met Glu Thr Gly Ser Leu Glu Lys Leu Leu Ala Ser Glu Pro  
100 105 110

Leu Pro Trp Asp Leu Arg Phe Arg Ile Ile His Glu Thr Ala Val Gly  
115 120 125

Met Asn Phe Leu His Cys Met Ala Pro Pro Leu Leu His Leu Asp Leu  
130 135 140

Lys Pro Ala Asn Ile Leu Leu Asp Ala His Tyr His Val Lys Ile Ser  
145 150 155 160

Asp Phe Gly Leu Ala Lys Cys Asn Gly Leu Ser His Ser His Asp Leu  
165 170 175

Ser Met Asp Gly Leu Phe Gly Thr Ile Ala Tyr Leu Pro Pro Glu Arg  
180 185 190

Ile Arg Glu Lys Ser Arg Leu Phe Asp Thr Lys His Asp Val Tyr Ser  
195 200 205

Phe Ala Ile Val Ile Trp Gly Val Leu Thr Gln Lys Lys Pro Phe Ala  
210 215 220

Asp Glu Lys Asn Ile Leu His Ile Met Val Lys Val Val Lys Gly His  
225 230 235 240

Arg Pro Glu Leu Pro Pro Val Cys Arg Ala Arg Pro Arg Ala Cys Ser  
245 250 255

His Leu Ile Arg Leu Met Gln Arg Cys Trp Gln Gly Asp Pro Arg Val  
260 265 270

Arg Pro Thr Phe Gln Glu Ile Thr Ser Glu Thr Glu Asp Leu Cys Glu  
275 280 285

Lys Pro Asp Asp Glu Val Lys Glu Thr Ala His Asp Leu Asp Val Lys  
290 295 300



Ser Pro Pro Glu Pro Arg Ser Glu Val Val Pro Ala Arg Leu Lys Arg  
 305 310 315 320  
 Ala Ser Ala Pro Thr Phe Asp Asn Asp Tyr Ser Leu Ser Glu Leu Leu  
 325 330 335  
 Ser Gln Leu Asp Ser Gly Val Ser Gln Ala Val Glu Gly Pro Glu Glu  
 340 345 350  
 Leu Ser Arg Ser Ser Ser Glu Ser Lys Leu Pro Ser Ser Gly Ser Gly  
 355 360 365  
 Lys Arg Leu Ser Gly Val Ser Ser Val Asp Ser Ala Phe Ser Ser Arg  
 370 375 380  
 Gly Ser Leu Ser Leu Ser Phe Glu Arg Glu Pro Ser Thr Ser Asp Leu  
 385 390 395 400  
 Gly Thr Thr Asp Val Gln Lys Lys Lys Leu Val Asp Ala Ile Val Ser  
 405 410 415  
 Gly Asp Thr Ser Lys Leu Met Lys Ile Leu Gln Pro Gln Asp Val Asp  
 420 425 430  
 Leu Ala Leu Asp Ser Gly Ala Ser Leu Leu His Leu Ala Val Glu Ala  
 435 440 445  
 Gly Gln Glu Glu Cys Ala Lys Trp Leu Leu Leu Asn Asn Ala Asn Pro  
 450 455 460  
 Asn Leu Ser Asn Arg Arg Gly Ser Thr Pro Leu His Met Ala Val Glu  
 465 470 475 480  
 Arg Arg Val Arg Gly Val Val Glu Leu Leu Leu Ala Arg Lys Ile Ser  
 485 490 495  
 Val Asn Ala Lys Asp Glu Asp Gln Trp Thr Ala Leu His Phe Ala Ala  
 500 505 510  
 Gln Asn Gly Asp Glu Ser Ser Thr Arg Leu Leu Leu Glu Lys Asn Ala  
 515 520 525  
 Ser Val Asn Glu Val Asp Phe Glu Gly Arg Thr Pro Met His Val Ala

530

535

540

Cys Gln His Gly Gln Glu Asn Ile Val Arg Ile Leu Leu Arg Arg Gly  
 545 550 555 560

Val Asp Val Ser Leu Gln Gly Lys Asp Ala Trp Leu Pro Leu His Tyr  
 565 570 575

Ala Ala Trp Gln Gly His Leu Pro Ile Val Lys Leu Leu Ala Lys Gln  
 580 585 590

Pro Gly Val Ser Val Asn Ala Gln Thr Leu Asp Gly Arg Thr Pro Leu  
 595 600 605

His Leu Ala Ala Gln Arg Gly His Tyr Arg Val Ala Arg Ile Leu Ile  
 610 615 620

Asp Leu Cys Ser Asp Val Asn Val Cys Ser Leu Leu Ala Gln Thr Pro  
 625 630 635 640

Leu His Val Ala Ala Glu Thr Gly His Thr Ser Thr Ala Arg Leu Leu  
 645 650 655

Leu His Arg Gly Ala Gly Lys Lys Ala Val Thr Ser Asp Gly Tyr Thr  
 660 665 670

Ala Leu His Leu Ala Ala Arg Asn Gly His Leu Ala Thr Val Lys Leu  
 675 680 685

Leu Val Glu Glu Lys Ala Asp Val Leu Ala Arg Gly Pro Leu Asn Gln  
 690 695 700

Thr Ala Leu His Leu Ala Ala His Gly His Ser Glu Val Val Glu  
 705 710 715 720

Glu Leu Val Ser Ala Asp Val Ile Asp Leu Phe Asp Glu Gln Gly Leu  
 725 730 735

Ser Ala Leu His Leu Ala Ala Gln Gly Arg His Ala Gln Thr Val Glu  
 740 745 750

Thr Leu Leu Arg His Gly Ala His Ile Asn Leu Gln Ser Leu Lys Phe  
 755 760 765

Gln Gly Gly His Gly Pro Ala Ala Thr Leu Leu Arg Arg Ser Lys Thr  
 770 775 780

<210> 154  
 <211> 682  
 <212> PRT  
 <213> Homo sapiens

<400> 154

Met Gly Lys Lys Tyr Lys Asn Ile Val Leu Leu Lys Gly Leu Glu Val  
 1 5 10 15

Ile Asn Asp Tyr His Phe Arg Met Val Lys Ser Leu Leu Ser Asn Asp  
 20 25 30

Leu Lys Leu Asn Leu Lys Met Arg Glu Glu Tyr Asp Lys Ile Gln Ile  
 35 40 45

Ala Asp Leu Met Glu Glu Lys Phe Arg Gly Asp Ala Gly Leu Gly Lys  
 50 55 60

Leu Ile Lys Ile Phe Glu Asp Ile Pro Thr Leu Glu Asp Leu Ala Glu  
 65 70 75 80

Thr Leu Lys Lys Glu Lys Leu Lys Val Lys Gly Pro Ala Leu Ser Arg  
 85 90 95

Lys Arg Lys Lys Glu Val His Ala Thr Ser Pro Ala Pro Ser Thr Ser  
 100 105 110

Ser Thr Val Lys Thr Glu Gly Ala Glu Ala Thr Pro Gly Ala Gln Lys  
 115 120 125

Arg Lys Lys Ser Thr Lys Glu Lys Ala Gly Pro Lys Gly Ser Lys Val  
 130 135 140

Ser Glu Glu Gln Thr Gln Pro Pro Ser Pro Ala Gly Ala Gly Met Ser  
 145 150 155 160

Thr Ala Met Gly Arg Ser Pro Ser Pro Lys Thr Ser Leu Ser Ala Pro  
 165 170 175

Pro Asn Ser Ser Ser Thr Glu Asn Pro Lys Thr Val Ala Lys Cys Gln  
 180 185 190

Val Thr Pro Arg Arg Asn Val Leu Gln Lys Arg Pro Val Ile Val Lys  
 195 200 205

Val Leu Ser Thr Thr Lys Pro Phe Glu Tyr Glu Thr Pro Glu Met Glu  
 210 215 220

Lys Lys Ile Met Phe His Ala Thr Val Ala Thr Gln Thr Gln Phe Phe  
 225 230 235 240

His Val Lys Val Leu Asn Thr Ser Leu Lys Glu Lys Phe Asn Gly Lys  
 245 250 255

Lys Ile Ile Ile Ile Ser Asp Tyr Leu Glu Tyr Asp Ser Leu Leu Glu  
 260 265 270

Val Asn Glu Glu Ser Thr Val Ser Glu Ala Gly Pro Asn Gln Thr Phe  
 275 280 285

Glu Val Pro Asn Lys Ile Ile Asn Arg Ala Lys Glu Thr Leu Lys Ile  
 290 295 300

Asp Ile Leu His Lys Lys Gln Ala Ser Gly Asn Ile Val Tyr Gly Val Phe  
 305 310 315 320

Met Leu His Lys Lys Thr Val Asn Gln Lys Thr Thr Ile Tyr Glu Ile  
 325 330 335

Gln Asp Asp Arg Gly Lys Met Asp Val Val Gly Thr Gly Gln Cys His  
 340 345 350

Asn Ile Pro Cys Glu Glu Gly Asp Lys Leu Gln Leu Phe Cys Phe Arg  
 355 360 365

Leu Arg Lys Lys Asn Gln Met Ser Lys Leu Ile Ser Glu Met His Ser  
 370 375 380

Phe Ile Gln Ile Lys Lys Lys Thr Asn Pro Arg Asn Asn Asp Pro Lys  
 385 390 395 400

Ser Met Lys Leu Pro Gln Glu Gln Arg Gln Leu Pro Tyr Pro Ser Glu

405	410	415
Ala Ser Thr Thr Phe Pro Glu Ser His Leu Arg Thr Pro Gln Met Pro		
420	425	430
Pro Thr Thr Pro Ser Ser Ser Phe Phe Thr Lys Lys Ser Glu Asp Thr		
435	440	445
Ile Ser Lys Met Asn Asp Phe Met Arg Met Gln Ile Leu Lys Glu Gly		
450	455	460
Ser His Phe Pro Gly Pro Phe Met Thr Ser Ile Gly Pro Ala Glu Ser		
465	470	475
His Pro His Thr Pro Gln Met Pro Pro Ser Thr Pro Ser Ser Ser Phe		
485	490	495
Leu Thr Thr Leu Lys Pro Arg Leu Lys Thr Glu Pro Glu Glu Val Ser		
500	505	510
Ile Glu Asp Ser Ala Gln Ser Asp Leu Lys Glu Val Met Val Leu Asn		
515	520	525
Ala Thr Glu Ser Phe Val Tyr Glu Pro Lys Glu Gln Lys Lys Met Phe		
530	535	540
His Ala Thr Val Ala Thr Glu Asn Glu Val Phe Arg Val Lys Val Phe		
545	550	555
Asn Ile Asp Leu Lys Glu Lys Phe Thr Pro Lys Lys Ile Ile Ala Ile		
565	570	575
Ala Asn Tyr Val Cys Arg Asn Gly Phe Leu Glu Val Tyr Pro Phe Thr		
580	585	590
Leu Val Ala Asp Val Asn Ala Asp Arg Asn Met Glu Ile Pro Lys Gly		
595	600	605
Leu Ile Arg Ser Ala Ser Val Thr Pro Lys Ile Asn Gln Leu Cys Ser		
610	615	620
Gln Thr Lys Gly Ser Phe Val Asn Gly Val Phe Glu Val His Lys Val		
625	630	635
		640

Ser Pro His His Cys Phe Ile Lys Phe Leu Leu Gln Pro Pro Ile Phe  
 645 650 655

Lys Val Leu Thr Cys Gln Leu Glu Phe Gly Gln Leu Thr Gln His Arg  
 660 665 670

Lys Ser Thr Pro Ser Pro Phe Pro Gln His  
 675 680

<210> 155  
 <211> 1218  
 <212> PRT  
 <213> Homo sapiens

<400> 155

Met Arg Ser Pro Arg Thr Arg Gly Arg Ser Gly Arg Pro Leu Ser Leu  
 1 5 10 15

Leu Leu Ala Leu Leu Cys Ala Leu Arg Ala Lys Val Cys Gly Ala Ser  
 20 25 30

Gly Gln Phe Glu Leu Glu Ile Leu Ser Met Gln Asn Val Asn Gly Glu  
 35 40 45

Leu Gln Asn Gly Asn Cys Cys Gly Gly Ala Arg Asn Pro Gly Asp Arg  
 50 55 60

Lys Cys Thr Arg Asp Glu Cys Asp Thr Tyr Phe Lys Val Cys Leu Lys  
 65 70 75 80

Glu Tyr Gln Ser Arg Val Thr Ala Gly Gly Pro Cys Ser Phe Gly Ser  
 85 90 95

Gly Ser Thr Pro Val Ile Gly Gly Asn Thr Phe Asn Leu Lys Ala Ser  
 100 105 110

Arg Gly Asn Asp Arg Asn Arg Ile Val Leu Pro Phe Ser Phe Ala Trp  
 115 120 125

Pro Arg Ser Tyr Thr Leu Leu Val Glu Ala Trp Asp Ser Ser Asn Asp  
 130 135 140

Thr Val Gln Pro Asp Ser Ile Ile Glu Lys Ala Ser His Ser Gly Met  
145 150 155 160

Ile Asn Pro Ser Arg Gln Trp Gln Thr Leu Lys Gln Asn Thr Gly Val  
165 170 175

Ala His Phe Glu Tyr Gln Ile Arg Val Thr Cys Asp Asp Tyr Tyr Tyr  
180 185 190

Gly Phe Gly Cys Asn Lys Phe Cys Arg Pro Arg Asp Asp Phe Phe Gly  
195 200 205

His Tyr Ala Cys Asp Gln Asn Gly Asn Lys Thr Cys Met Glu Gly Trp  
210 215 220

Met Gly Pro Glu Cys Asn Arg Ala Ile Cys Arg Gln Gly Cys Ser Pro  
225 230 235 240

Lys His Gly Ser Cys Lys Leu Pro Gly Asp Cys Arg Cys Gln Tyr Gly  
245 250 255

Trp Gln Gly Leu Tyr Cys Asp Lys Cys Ile Pro His Pro Gly Cys Val  
260 265 270

His Gly Ile Cys Asn Glu Pro Trp Gln Cys Leu Cys Glu Thr Asn Trp  
275 280 285

Gly Gly Gln Leu Cys Asp Lys Asp Leu Asn Tyr Cys Gly Thr His Gln  
290 295 300

Pro Cys Leu Asn Gly Gly Thr Cys Ser Asn Thr Gly Pro Asp Lys Tyr  
305 310 315 320

Gln Cys Ser Cys Pro Glu Gly Tyr Ser Gly Pro Asn Cys Glu Ile Ala  
325 330 335

Glu His Ala Cys Leu Ser Asp Pro Cys His Asn Arg Gly Ser Cys Lys  
340 345 350

Glu Thr Ser Leu Gly Phe Glu Cys Glu Cys Ser Pro Gly Trp Thr Gly  
355 360 365

Pro Thr Cys Ser Thr Asn Ile Asp Asp Cys Ser Pro Asn Asn Cys Ser

370

375

380

His Gly Gly Thr Cys Gln Asp Leu Val Asn Gly Phe Lys Cys Val Cys  
 385 390 395 400

Pro Pro Gln Trp Thr Gly Lys Thr Cys Gln Leu Asp Ala Asn Glu Cys  
 405 410 415

Glu Ala Lys Pro Cys Val Asn Ala Lys Ser Cys Lys Asn Leu Ile Ala  
 420 425 430

Ser Tyr Tyr Cys Asp Cys Leu Pro Gly Trp Met Gly Gln Asn Cys Asp  
 435 440 445

Ile Asn Ile Asn Asp Cys Leu Gly Gln Cys Gln Asn Asp Ala Ser Cys  
 450 455 460

Arg Asp Leu Val Asn Gly Tyr Arg Cys Ile Cys Pro Pro Gly Tyr Ala  
 465 470 475 480

Gly Asp His Cys Glu Arg Asp Ile Asp Glu Cys Ala Ser Asn Pro Cys  
 485 490 495

Leu Asn Gly Gly His Cys Gln Asn Glu Ile Asn Arg Phe Gln Cys Leu  
 500 505 510

Cys Pro Thr Gly Phe Ser Gly Asn Leu Cys Gln Leu Asp Ile Asp Tyr  
 515 520 525

Cys Glu Pro Asn Pro Cys Gln Asn Gly Ala Gln Cys Tyr Asn Arg Ala  
 530 535 540

Ser Asp Tyr Phe Cys Lys Cys Pro Glu Asp Tyr Glu Gly Lys Asn Cys  
 545 550 555 560

Ser His Leu Lys Asp His Cys Arg Thr Thr Pro Cys Glu Val Ile Asp  
 565 570 575

Ser Cys Thr Val Ala Met Ala Ser Asn Asp Thr Pro Glu Gly Val Arg  
 580 585 590

Tyr Ile Ser Ser Asn Val Cys Gly Pro His Gly Lys Cys Lys Ser Gln  
 595 600 605



Ser Gly Gly Lys Phe Thr Cys Asp Cys Asn Lys Gly Phe Thr Gly Thr  
610 615 620

Tyr Cys His Glu Asn Ile Asn Asp Cys Glu Ser Asn Pro Cys Arg Asn  
625 630 635 640

Gly Gly Thr Cys Ile Asp Gly Val Asn Ser Tyr Lys Cys Ile Cys Ser  
645 650 655

Asp Gly Trp Glu Gly Ala Tyr Cys Glu Thr Asn Ile Asn Asp Cys Ser  
660 665 670

Gln Asn Pro Cys His Asn Gly Gly Thr Cys Arg Asp Leu Val Asn Asp  
675 680 685

Phe Tyr Cys Asp Cys Lys Asn Gly Trp Lys Gly Lys Thr Cys His Ser  
690 695 700

Arg Asp Ser Gln Cys Asp Glu Ala Thr Cys Asn Asn Gly Gly Thr Cys  
705 710 715 720

Tyr Asp Glu Gly Asp Ala Phe Lys Cys Met Cys Pro Gly Gly Trp Glu  
725 730 735

Gly Thr Thr Cys Asn Ile Ala Arg Asn Ser Ser Cys Leu Pro Asn Pro  
740 745 750

Cys His Asn Gly Gly Thr Cys Val Val Asn Gly Glu Ser Phe Thr Cys  
755 760 765

Val Cys Lys Glu Gly Trp Glu Gly Pro Ile Cys Ala Gln Asn Thr Asn  
770 775 780

Asp Cys Ser Pro His Pro Cys Tyr Asn Ser Gly Thr Cys Val Asp Gly  
785 790 795 800

Asp Asn Trp Tyr Arg Cys Glu Cys Ala Pro Gly Phe Ala Gly Pro Asp  
805 810 815

Cys Arg Ile Asn Ile Asn Glu Cys Gln Ser Ser Pro Cys Ala Phe Gly  
820 825 830

Ala Thr Cys Val Asp Glu Ile Asn Gly Tyr Arg Cys Val Cys Pro Pro  
 835 840 845

Gly His Ser Gly Ala Lys Cys Gln Glu Val Ser Gly Arg Pro Cys Ile  
 850 855 860

Thr Met Gly Ser Val Ile Pro Asp Gly Ala Lys Trp Asp Asp Asp Cys  
 865 870 875 880

Asn Thr Cys Gln Cys Leu Asn Gly Arg Ile Ala Cys Ser Lys Val Trp  
 885 890 895

Cys Gly Pro Arg Pro Cys Leu Leu His Lys Gly His Ser Glu Cys Pro  
 900 905 910

Ser Gly Gln Ser Cys Ile Pro Ile Leu Asp Asp Gln Cys Phe Val His  
 915 920 925

Pro Cys Thr Gly Val Gly Glu Cys Arg Ser Ser Ser Leu Gln Pro Val  
 930 935 940

Lys Thr Lys Cys Thr Ser Asp Ser Tyr Tyr Gln Asp Asn Cys Ala Asn  
 945 950 955 960

Ile Thr Phe Thr Phe Asn Lys Glu Met Met Ser Pro Gly Leu Thr Thr  
 965 970 975

Glu His Ile Cys Ser Glu Leu Arg Asn Leu Asn Ile Leu Lys Asn Val  
 980 985 990

Ser Ala Glu Tyr Ser Ile Tyr Ile Ala Cys Glu Pro Ser Pro Ser Ala  
 995 1000 1005

Asn Asn Glu Ile His Val Ala Ile Ser Ala Glu Asp Ile Arg Asp  
 1010 1015 1020

Asp Gly Asn Pro Ile Lys Glu Ile Thr Asp Lys Ile Ile Asp Leu  
 1025 1030 1035

Val Ser Lys Arg Asp Gly Asn Ser Ser Leu Ile Ala Ala Val Ala  
 1040 1045 1050

Glu Val Arg Val Gln Arg Arg Pro Leu Lys Asn Arg Thr Asp Phe  
 1055 1060 1065

Leu Val Pro Leu Leu Ser Ser Val Leu Thr Val Ala Trp Ile Cys  
 1070 1075 1080

Cys Leu Val Thr Ala Phe Tyr Trp Cys Leu Arg Lys Arg Arg Lys  
 1085 1090 1095

Pro Gly Ser His Thr His Ser Ala Ser Glu Asp Asn Thr Thr Asn  
 1100 1105 1110

Asn Val Arg Glu Gln Leu Asn Gln Ile Lys Asn Pro Ile Glu Lys  
 1115 1120 1125

His Gly Ala Asn Thr Val Pro Ile Lys Asp Tyr Glu Asn Lys Asn  
 1130 1135 1140

Ser Lys Met Ser Lys Ile Arg Thr His Asn Ser Glu Val Glu Glu  
 1145 1150 1155

Asp Asp Met Asp Lys His Gln Gln Lys Ala Arg Phe Ala Lys Gln  
 1160 1165 1170

Pro Ala Tyr Thr Leu Val Asp Arg Glu Glu Lys Pro Pro Asn Gly  
 1175 1180 1185

Thr Pro Thr Lys His Pro Asn Trp Thr Asn Lys Gln Asp Asn Arg  
 1190 1195 1200

Asp Leu Glu Ser Ala Gln Ser Leu Asn Arg Met Glu Tyr Ile Val  
 1205 1210 1215

<210> 156  
 <211> 334  
 <212> PRT  
 <213> Homo sapiens

<400> 156

Met Lys Met Ala Ser Ser Leu Ala Phe Leu Leu Leu Asn Phe His Val  
 1 5 10 15

Ser Leu Leu Leu Val Gln Leu Leu Thr Pro Cys Ser Ala Gln Phe Ser  
 20 25 30

Val Leu Gly Pro Ser Gly Pro Ile Leu Ala Met Val Gly Glu Asp Ala  
 35 40 45

Asp Leu Pro Cys His Leu Phe Pro Thr Met Ser Ala Glu Thr Met Glu  
 50 55 60

Leu Lys Trp Val Ser Ser Ser Leu Arg Gln Val Val Asn Val Tyr Ala  
 65 70 75 80

Asp Gly Lys Glu Val Glu Asp Arg Gln Ser Ala Pro Tyr Arg Gly Arg  
 85 90 95

Thr Ser Ile Leu Arg Asp Gly Ile Thr Ala Gly Lys Ala Ala Leu Arg  
 100 105 110

Ile His Asn Val Thr Ala Ser Asp Ser Gly Lys Tyr Leu Cys Tyr Phe  
 115 120 125

Gln Asp Gly Asp Phe Tyr Glu Lys Ala Leu Val Glu Leu Lys Val Ala  
 130 135 140

Ala Leu Gly Ser Asn Leu His Val Glu Val Lys Gly Tyr Glu Asp Gly  
 145 150 155 160

Gly Ile His Leu Glu Cys Arg Ser Thr Gly Trp Tyr Pro Gln Pro Gln  
 165 170 175

Ile Gln Trp Gly Asn Ala Lys Gly Glu Asn Ile Pro Ala Val Glu Ala  
 180 185 190

Pro Val Val Ala Asp Gly Val Gly Leu Tyr Glu Val Ala Ala Ser Val  
 195 200 205

Ile Met Lys Ser Gly Ser Gly Glu Gly Val Ser Cys Ile Ile Arg Asn  
 210 215 220

Ser Leu Leu Gly Leu Glu Lys Thr Ala Ser Ile Ser Ile Ala Asp Pro  
 225 230 235 240

Phe Phe Arg Ser Ala Gln Pro Trp Ile Ala Ala Leu Ala Gly Thr Leu  
 245 250 255

Pro Ile Leu Leu Leu Leu Leu Ala Gly Ala Ser Tyr Phe Leu Trp Arg  
                   260                  265                  270

Gln Gln Lys Glu Ile Thr Ala Leu Ser Ser Glu Ile Glu Ser Glu Gln  
                   275                  280                  285

Glu Met Lys Glu Met Gly Tyr Ala Ala Thr Glu Arg Glu Ile Ser Leu  
                   290                  295                  300

Arg Glu Ser Leu Gln Glu Glu Leu Lys Arg Lys Lys Ile Gln Tyr Leu  
                   305                  310                  315                  320

Thr Arg Gly Glu Glu Ser Ser Ser Asp Thr Asn Lys Ser Ala  
                                   325                                  330

<210> 157  
 <211> 584  
 <212> PRT  
 <213> Homo sapiens

<400> 157

Met Lys Met Ala Ser Ser Leu Ala Phe Leu Leu Leu Asn Phe His Val  
   1                  5                  10                  15

Ser Leu Phe Leu Val Gln Leu Leu Thr Pro Cys Ser Ala Gln Phe Ser  
                   20                  25                  30

Val Leu Gly Pro Ser Gly Pro Ile Leu Ala Met Val Gly Glu Asp Ala  
                   35                  40                  45

Asp Leu Pro Cys His Leu Phe Pro Thr Met Ser Ala Glu Thr Met Glu  
                   50                  55                  60

Leu Arg Trp Val Ser Ser Ser Leu Arg Gln Val Val Asn Val Tyr Ala  
   65                  70                  75                  80

Asp Gly Lys Glu Val Glu Asp Arg Gln Ser Ala Pro Tyr Arg Gly Arg  
                   85                  90                  95

Thr Ser Ile Leu Arg Asp Gly Ile Thr Ala Gly Lys Ala Ala Leu Arg  
                   100                  105                  110

Ile His Asn Val Thr Ala Ser Asp Ser Gly Lys Tyr Leu Cys Tyr Phe

115                                      120                                      125  
 Gln Asp Gly Asp Phe Tyr Glu Lys Ala Leu Val Glu Leu Lys Val Ala  
 130                                      135                                      140  
 Ala Leu Gly Ser Asp Leu His Ile Glu Val Lys Gly Tyr Glu Asp Gly  
 145                                      150                                      155                                      160  
 Gly Ile His Leu Glu Cys Arg Ser Thr Gly Trp Tyr Pro Gln Pro Gln  
 165                                      170                                      175  
 Ile Lys Trp Ser Asp Thr Lys Gly Glu Asn Ile Pro Ala Val Glu Ala  
 180                                      185                                      190  
 Pro Val Val Ala Asp Gly Val Gly Leu Tyr Ala Val Ala Ala Ser Val  
 195                                      200                                      205  
 Ile Met Arg Gly Ser Ser Gly Gly Gly Val Ser Cys Ile Ile Arg Asn  
 210                                      215                                      220  
 Ser Leu Leu Gly Leu Glu Lys Thr Ala Ser Ile Ser Ile Ala Asp Pro  
 225                                      230                                      235                                      240  
 Phe Phe Arg Ser Ala Gln Pro Trp Ile Ala Ala Leu Ala Gly Thr Leu  
 245                                      250                                      255  
 Pro Ile Ser Leu Leu Leu Leu Ala Gly Ala Ser Tyr Phe Leu Trp Arg  
 260                                      265                                      270  
 Gln Gln Lys Glu Lys Ile Ala Leu Ser Arg Glu Thr Glu Arg Glu Arg  
 275                                      280                                      285  
 Glu Met Lys Glu Met Gly Tyr Ala Ala Thr Glu Gln Glu Ile Ser Leu  
 290                                      295                                      300  
 Arg Glu Lys Leu Gln Glu Glu Leu Lys Trp Arg Lys Ile Gln Tyr Met  
 305                                      310                                      315                                      320  
 Ala Arg Gly Glu Lys Ser Leu Ala Tyr His Glu Trp Lys Met Ala Leu  
 325                                      330                                      335  
 Phe Lys Pro Ala Asp Val Ile Leu Asp Pro Asp Thr Ala Asn Ala Ile  
 340                                      345                                      350

Leu Leu Val Ser Glu Asp Gln Arg Ser Val Gln Arg Ala Glu Glu Pro  
 355 360 365

Arg Asp Leu Pro Asp Asn Pro Glu Arg Phe Glu Trp Arg Tyr Cys Val  
 370 375 380

Leu Gly Cys Glu Asn Phe Thr Ser Gly Arg His Tyr Trp Glu Val Glu  
 385 390 395 400

Val Gly Asp Arg Lys Glu Trp His Ile Gly Val Cys Ser Lys Asn Val  
 405 410 415

Glu Arg Lys Lys Gly Trp Val Lys Met Thr Pro Glu Asn Gly Tyr Trp  
 420 425 430

Thr Met Gly Leu Thr Asp Gly Asn Lys Tyr Arg Ala Leu Thr Glu Pro  
 435 440 445

Arg Thr Asn Leu Lys Leu Pro Glu Pro Pro Arg Lys Val Gly Ile Phe  
 450 455 460

Leu Asp Tyr Glu Thr Gly Glu Ile Ser Phe Tyr Asn Ala Thr Asp Gly  
 465 470 475 480

Ser His Ile Tyr Thr Phe Pro His Ala Ser Phe Ser Glu Pro Leu Tyr  
 485 490 495

Pro Val Phe Arg Ile Leu Thr Leu Glu Pro Thr Ala Leu Thr Ile Cys  
 500 505 510

Pro Ile Pro Lys Glu Val Glu Ser Ser Pro Asp Pro Asp Leu Val Pro  
 515 520 525

Asp His Ser Leu Glu Thr Pro Leu Thr Pro Gly Leu Ala Asn Glu Ser  
 530 535 540

Gly Glu Pro Gln Ala Glu Val Thr Ser Leu Leu Leu Pro Ala His Pro  
 545 550 555 560

Gly Ala Glu Val Ser Pro Ser Ala Thr Thr Asn Gln Asn His Lys Leu  
 565 570 575

Gln Ala Arg Thr Glu Ala Leu Tyr  
580

<210> 158  
<211> 708  
<212> PRT  
<213> Homo sapiens

<400> 158

Met Asn Pro Thr Glu Thr Lys Ala Ile Pro Val Ser Gln Gln Met Glu  
1 5 10 15

Gly Pro His Leu Pro Asn Lys Lys Lys His Lys Lys Gln Ala Val Lys  
20 25 30

Thr Glu Pro Glu Lys Lys Ser Gln Ser Thr Lys Leu Ser Val Val His  
35 40 45

Glu Lys Lys Ser Gln Glu Gly Lys Pro Lys Glu His Thr Glu Pro Lys  
50 55 60

Ser Leu Pro Lys Gln Ala Ser Asp Thr Gly Ser Asn Asp Ala His Asn  
65 70 75 80

Lys Lys Ala Val Ser Arg Ser Ala Glu Gln Gln Pro Ser Glu Lys Ser  
85 90 95

Thr Glu Pro Lys Thr Lys Pro Gln Asp Met Ile Ser Ala Gly Gly Glu  
100 105 110

Ser Val Ala Gly Ile Thr Ala Ile Ser Gly Lys Pro Gly Asp Lys Lys  
115 120 125

Lys Glu Lys Lys Ser Leu Thr Pro Ala Val Pro Val Glu Ser Lys Pro  
130 135 140

Asp Lys Pro Ser Gly Lys Ser Gly Met Asp Ala Ala Leu Asp Asp Leu  
145 150 155 160

Ile Asp Thr Leu Gly Gly Pro Glu Glu Thr Glu Glu Glu Asn Thr Thr  
165 170 175

Tyr Thr Gly Pro Glu Val Ser Asp Pro Met Ser Ser Thr Tyr Ile Glu



180	185	190
Glu Leu Gly Lys Arg Glu Val Thr Ile Pro Pro Lys Tyr Arg Glu Leu		
195	200	205
Leu Ala Lys Lys Glu Gly Ile Thr Gly Pro Pro Ala Asp Ser Ser Lys		
210	215	220
Pro Ile Gly Pro Asp Asp Ala Ile Asp Ala Leu Ser Ser Asp Phe Thr		
225	230	235
Cys Gly Ser Pro Thr Ala Ala Gly Lys Lys Thr Glu Lys Glu Glu Ser		
245	250	255
Thr Glu Val Leu Lys Ala Gln Ser Ala Gly Thr Val Arg Ser Ala Ala		
260	265	270
Pro Pro Gln Glu Lys Lys Arg Lys Val Glu Lys Asp Thr Met Ser Asp		
275	280	285
Gln Ala Leu Glu Ala Leu Ser Ala Ser Leu Gly Thr Arg Gln Ala Glu		
290	295	300
Pro Glu Leu Asp Leu Arg Ser Ile Lys Glu Val Asp Glu Ala Lys Ala		
305	310	315
Lys Glu Glu Lys Leu Glu Lys Cys Gly Glu Asp Asp Glu Thr Ile Pro		
325	330	335
Ser Glu Tyr Arg Leu Lys Pro Ala Thr Asp Lys Asp Gly Lys Pro Leu		
340	345	350
Leu Pro Glu Pro Glu Glu Lys Pro Lys Pro Arg Ser Glu Ser Glu Leu		
355	360	365
Ile Asp Glu Leu Ser Glu Asp Phe Asp Arg Ser Glu Cys Lys Glu Lys		
370	375	380
Pro Ser Lys Pro Thr Glu Lys Thr Glu Glu Ser Lys Ala Ala Ala Pro		
385	390	395
Ala Pro Val Ser Glu Ala Val Cys Arg Thr Ser Met Cys Ser Ile Gln		
405	410	415

Ser Ala Pro Pro Glu Pro Ala Thr Leu Lys Gly Thr Val Pro Asp Asp  
 420 425 430

Ala Val Glu Ala Leu Ala Asp Ser Leu Gly Lys Lys Glu Ala Asp Pro  
 435 440 445

Glu Asp Gly Lys Pro Val Met Asp Lys Val Lys Glu Lys Ala Lys Glu  
 450 455 460

Glu Asp Arg Glu Lys Leu Gly Glu Lys Glu Glu Thr Ile Pro Pro Asp  
 465 470 475 480

Tyr Arg Leu Glu Glu Val Lys Asp Lys Asp Gly Lys Pro Leu Leu Pro  
 485 490 495

Lys Glu Ser Lys Glu Gln Leu Pro Pro Met Ser Glu Asp Phe Leu Leu  
 500 505 510

Asp Ala Leu Ser Glu Asp Phe Ser Gly Pro Gln Asn Ala Ser Ser Leu  
 515 520 525

Lys Phe Glu Asp Ala Lys Leu Ala Ala Ala Ile Ser Glu Val Val Ser  
 530 535 540

Gln Thr Pro Ala Ser Thr Thr Gln Ala Gly Ala Pro Pro Arg Asp Thr  
 545 550 555 560

Ser Gln Ser Asp Lys Asp Leu Asp Asp Ala Leu Asp Lys Leu Ser Asp  
 565 570 575

Ser Leu Gly Gln Arg Gln Pro Asp Pro Asp Glu Asn Lys Pro Met Glu  
 580 585 590

Asp Lys Val Lys Glu Lys Ala Lys Ala Glu His Arg Asp Lys Leu Gly  
 595 600 605

Glu Arg Asp Asp Thr Ile Pro Pro Glu Tyr Arg His Leu Leu Asp Asp  
 610 615 620

Asn Gly Gln Asp Lys Pro Val Lys Pro Pro Thr Lys Lys Ser Glu Asp  
 625 630 635 640

Ser Lys Lys Pro Ala Asp Asp Gln Asp Pro Ile Asp Ala Leu Ser Gly  
645 650 655

Asp Leu Asp Ser Cys Pro Ser Thr Thr Glu Thr Ser Gln Asn Thr Ala  
660 665 670

Lys Asp Lys Cys Lys Lys Ala Ala Ser Ser Ser Lys Ala Pro Lys Asn  
675 680 685

Gly Gly Lys Ala Lys Asp Ser Ala Lys Thr Thr Glu Glu Thr Ser Lys  
690 695 700

Pro Lys Asp Asp  
705

<210> 159  
<211> 395  
<212> PRT  
<213> Homo sapiens  
  
<400> 159

Met Trp Leu Pro Arg Val Ser Ser Thr Ala Val Thr Ala Leu Leu Leu  
1 5 10 15

Ala Gln Thr Phe Leu Leu Leu Phe Leu Val Ser Arg Pro Gly Pro Ser  
20 25 30

Ser Pro Ala Gly Gly Glu Ala Arg Val His Val Leu Val Leu Ser Ser  
35 40 45

Trp Arg Ser Gly Ser Ser Phe Val Gly Gln Leu Phe Asn Gln His Pro  
50 55 60

Asp Val Phe Tyr Leu Met Glu Pro Ala Trp His Val Trp Thr Thr Leu  
65 70 75 80

Ser Gln Gly Ser Ala Ala Thr Leu His Met Ala Val Arg Asp Leu Val  
85 90 95

Arg Ser Val Phe Leu Cys Asp Met Asp Val Phe Asp Ala Tyr Leu Pro  
100 105 110

Trp Arg Arg Asn Leu Ser Asp Leu Phe Gln Trp Ala Val Ser Arg Ala

115	120	125
Leu Cys Ser Pro Pro Ala Cys Ser Ala Phe Pro Arg Gly Ala Ile Ser		
130	135	140
Ser Glu Ala Val Cys Lys Pro Leu Cys Ala Arg Gln Ser Phe Thr Leu		
145	150	155
Ala Arg Glu Ala Cys Arg Ser Tyr Ser His Val Val Leu Lys Glu Val		
165	170	175
Arg Phe Phe Asn Leu Gln Val Leu Tyr Pro Leu Leu Ser Asp Pro Ala		
180	185	190
Leu Asn Leu Arg Ile Val His Leu Val Arg Asp Pro Arg Ala Val Leu		
195	200	205
Arg Ser Arg Glu Gln Thr Ala Lys Ala Leu Ala Arg Asp Asn Gly Ile		
210	215	220
Val Leu Gly Thr Asn Gly Thr Trp Val Glu Ala Asp Pro Gly Leu Arg		
225	230	235
Val Val Arg Glu Val Cys Arg Ser His Val Arg Ile Ala Glu Ala Ala		
245	250	255
Thr Leu Lys Pro Pro Pro Phe Leu Arg Gly Arg Tyr Arg Leu Val Arg		
260	265	270
Phe Glu Asp Leu Ala Arg Glu Pro Leu Ala Glu Ile Arg Ala Leu Tyr		
275	280	285
Ala Phe Thr Gly Leu Ser Leu Thr Pro Gln Leu Glu Ala Trp Ile His		
290	295	300
Asn Ile Thr His Gly Ser Gly Pro Gly Ala Arg Arg Glu Ala Phe Lys		
305	310	315
Thr Ser Ser Arg Asn Ala Leu Asn Val Ser Gln Ala Trp Arg His Ala		
325	330	335
Leu Pro Phe Ala Lys Ile Arg Arg Val Gln Glu Leu Cys Ala Gly Ala		
340	345	350

Leu Gln Leu Leu Gly Tyr Arg Pro Val Tyr Ser Glu Asp Glu Gln Arg  
 355 360 365

Asn Leu Ala Leu Asp Leu Val Leu Pro Arg Gly Leu Asn Gly Phe Thr  
 370 375 380

Trp Ala Ser Ser Thr Ala Ser His Pro Arg Asn  
 385 390 395

<210> 160  
 <211> 254  
 <212> PRT  
 <213> Homo sapiens

<400> 160

Met Pro Ala Lys Thr Pro Ile Tyr Leu Lys Ala Ala Asn Asn Lys Lys  
 1 5 10 15

Gly Lys Lys Phe Lys Leu Arg Asp Ile Leu Ser Pro Asp Met Ile Ser  
 20 25 30

Pro Pro Leu Gly Asp Phe Arg His Thr Ile His Ile Gly Lys Glu Gly  
 35 40 45

Gln His Asp Val Phe Gly Asp Ile Ser Phe Leu Gln Gly Asn Tyr Glu  
 50 55 60

Leu Leu Pro Gly Asn Gln Glu Lys Ala His Leu Gly Gln Phe Pro Gly  
 65 70 75 80

His Asn Glu Phe Phe Arg Ala Asn Ser Thr Ser Asp Ser Val Phe Thr  
 85 90 95

Glu Thr Pro Ser Pro Val Leu Lys Asn Ala Ile Ser Leu Pro Thr Ile  
 100 105 110

Gly Gly Ser Gln Ala Leu Met Leu Pro Leu Leu Ser Pro Val Thr Phe  
 115 120 125

Asn Ser Lys Gln Glu Ser Phe Gly Pro Ala Lys Leu Pro Arg Leu Ser  
 130 135 140

Cys Glu Pro Val Met Glu Glu Lys Ala Gln Glu Lys Ser Ser Leu Leu  
 145 150 155 160

Glu Asn Gly Thr Val His Gln Gly Asp Thr Ser Trp Gly Ser Ser Gly  
 165 170 175

Ser Ala Ser Gln Ser Ser Gln Gly Arg Asp Ser His Ser Ser Ser Leu  
 180 185 190

Ser Glu Gln Tyr Pro Asp Trp Pro Ala Glu Asp Met Phe Asp His Pro  
 195 200 205

Thr Pro Cys Glu Leu Ile Lys Gly Lys Thr Lys Ser Glu Glu Ser Leu  
 210 215 220

Ser Asp Leu Thr Gly Ser Leu Leu Ser Leu Gln Leu Asp Leu Gly Pro  
 225 230 235 240

Ser Leu Leu Asp Glu Val Leu Asn Val Met Asp Lys Asn Lys  
 245 250

<210> 161  
 <211> 536  
 <212> PRT  
 <213> Homo sapiens

<400> 161

Met Asp Lys Val Gly Lys Met Trp Asn Asn Phe Lys Tyr Arg Cys Gln  
 1 5 10 15

Asn Leu Phe Gly His Glu Gly Gly Ser Arg Ser Glu Asn Val Asp Met  
 20 25 30

Asn Ser Asn Arg Cys Leu Ser Val Lys Glu Lys Asn Ile Ser Ile Gly  
 35 40 45

Asp Ser Thr Pro Gln Gln Gln Ser Ser Pro Leu Arg Glu Asn Ile Ala  
 50 55 60

Leu Gln Leu Gly Leu Ser Pro Ser Lys Asn Ser Ser Arg Arg Asn Gln  
 65 70 75 80

Asn Cys Ala Thr Glu Ile Pro Gln Ile Val Glu Ile Ser Ile Glu Lys  
 85 90 95

Asp Asn Asp Ser Cys Val Thr Pro Gly Thr Arg Leu Ala Arg Arg Asp  
 100 105 110

Ser Tyr Ser Arg His Ala Pro Trp Gly Gly Lys Lys Lys His Ser Cys  
 115 120 125

Ser Thr Lys Thr Gln Ser Ser Leu Asp Ala Asp Lys Lys Phe Gly Arg  
 130 135 140

Thr Arg Ser Gly Leu Gln Arg Arg Glu Arg Arg Tyr Gly Val Ser Ser  
 145 150 155 160

Val His Asp Met Asp Ser Val Ser Ser Arg Thr Val Gly Ser Arg Ser  
 165 170 175

Leu Arg Gln Arg Leu Gln Asp Thr Val Gly Leu Cys Phe Pro Met Arg  
 180 185 190

Thr Tyr Ser Lys Gln Ser Lys Pro Leu Phe Ser Asn Lys Arg Lys Ile  
 195 200 205

His Leu Ser Glu Leu Met Leu Glu Lys Cys Pro Phe Pro Ala Gly Ser  
 210 215 220

Asp Leu Ala Gln Lys Trp His Leu Ile Lys Gln His Thr Ala Pro Val  
 225 230 235 240

Ser Pro His Ser Thr Phe Phe Asp Thr Phe Asp Pro Ser Leu Val Ser  
 245 250 255

Thr Glu Asp Glu Glu Asp Arg Leu Arg Glu Arg Arg Arg Leu Ser Ile  
 260 265 270

Glu Glu Gly Val Asp Pro Pro Pro Asn Ala Gln Ile His Thr Phe Glu  
 275 280 285

Ala Thr Ala Gln Val Asn Pro Leu Tyr Lys Leu Gly Pro Lys Leu Ala  
 290 295 300

Pro Gly Met Thr Glu Ile Ser Gly Asp Ser Ser Ala Ile Pro Gln Ala  
 305 310 315 320

Asn Cys Asp Ser Glu Glu Asp Thr Thr Thr Leu Cys Leu Gln Ser Arg  
 325 330 335

Arg Gln Lys Gln Arg Gln Ile Ser Gly Asp Ser His Thr His Val Ser  
 340 345 350

Arg Gln Gly Ala Trp Lys Val His Thr Gln Ile Asp Tyr Ile His Cys  
 355 360 365

Leu Val Pro Asp Leu Leu Gln Ile Thr Gly Asn Pro Cys Tyr Trp Gly  
 370 375 380

Val Met Asp Arg Tyr Glu Ala Glu Ala Leu Leu Glu Gly Lys Pro Glu  
 385 390 395 400

Gly Thr Phe Leu Leu Arg Asp Ser Ala Gln Glu Asp Tyr Leu Phe Ser  
 405 410 415

Val Ser Phe Arg Arg Tyr Asn Arg Ser Leu His Ala Arg Ile Glu Gln  
 420 425 430

Trp Asn His Asn Phe Ser Phe Asp Ala His Asp Pro Cys Val Phe His  
 435 440 445

Ser Ser Thr Val Thr Gly Leu Leu Glu His Tyr Lys Asp Pro Ser Ser  
 450 455 460

Cys Met Phe Phe Glu Pro Leu Leu Thr Ile Ser Leu Asn Arg Thr Phe  
 465 470 475 480

Pro Phe Ser Leu Gln Tyr Ile Cys Arg Ala Val Ile Cys Arg Cys Thr  
 485 490 495

Thr Tyr Asp Gly Ile Asp Gly Leu Pro Leu Pro Ser Met Leu Gln Asp  
 500 505 510

Phe Leu Lys Glu Tyr His Tyr Lys Gln Lys Val Arg Val Arg Trp Leu  
 515 520 525

Glu Arg Glu Pro Val Lys Ala Lys  
 530 535



<210> 162  
 <211> 142  
 <212> PRT  
 <213> Homo sapiens

<400> 162

Met Ala Thr Lys Ile Asp Lys Glu Ala Cys Arg Ala Ala Tyr Asn Leu  
 1 5 10 15

Val Arg Asp Asp Gly Ser Ala Val Ile Trp Val Thr Phe Lys Tyr Asp  
 20 25 30

Gly Ser Thr Ile Val Pro Gly Glu Gln Gly Ala Glu Tyr Gln His Phe  
 35 40 45

Ile Gln Gln Cys Thr Asp Asp Val Arg Leu Phe Ala Phe Val Arg Phe  
 50 55 60

Thr Thr Gly Asp Ala Met Ser Lys Arg Ser Lys Phe Ala Leu Ile Thr  
 65 70 75 80

Trp Ile Gly Glu Asn Val Ser Gly Leu Gln Arg Ala Lys Thr Gly Thr  
 85 90 95

Asp Lys Thr Leu Val Lys Glu Val Val Gln Asn Phe Ala Lys Glu Phe  
 100 105 110

Val Ile Ser Asp Arg Lys Glu Leu Glu Glu Asp Phe Ile Lys Ser Glu  
 115 120 125

Leu Lys Lys Ala Gly Gly Ala Asn Tyr Asp Ala Gln Thr Glu  
 130 135 140

<210> 163  
 <211> 658  
 <212> PRT  
 <213> Homo sapiens

<400> 163

Met Ala Glu Ala Ala Ala Ala Gly Gly Thr Gly Leu Gly Ala Gly  
 1 5 10 15

Ala Ser Tyr Gly Ser Ala Ala Asp Arg Asp Arg Asp Pro Asp Pro Asp  
 20 25 30

Arg Ala Gly Arg Arg Leu Arg Val Leu Ser Gly His Leu Leu Gly Arg  
 35 40 45

Pro Arg Glu Ala Leu Ser Thr Asn Glu Cys Lys Ala Arg Arg Ala Ala  
 50 55 60

Ser Ala Ala Thr Ala Ala Pro Thr Ala Thr Pro Ala Ala Gln Glu Ser  
 65 70 75 80

Gly Thr Ile Pro Lys Lys Arg Gln Glu Val Met Lys Trp Asn Gly Trp  
 85 90 95

Gly Tyr Asn Asp Ser Lys Phe Ile Phe Asn Lys Lys Gly Gln Ile Glu  
 100 105 110

Leu Thr Gly Lys Arg Tyr Pro Leu Ser Gly Met Gly Leu Pro Thr Phe  
 115 120 125

Lys Glu Trp Ile Gln Asn Thr Leu Gly Val Asn Val Glu His Lys Thr  
 130 135 140

Thr Ser Lys Ala Ser Leu Asn Pro Ser Asp Thr Pro Pro Ser Val Val  
 145 150 155 160

Asn Glu Asp Phe Leu His Asp Leu Lys Glu Thr Asn Ile Ser Tyr Ser  
 165 170 175

Gln Glu Ala Asp Asp Arg Val Phe Arg Ala His Gly His Cys Leu His  
 180 185 190

Glu Ile Phe Leu Leu Arg Glu Gly Met Phe Glu Arg Ile Pro Asp Ile  
 195 200 205

Val Leu Trp Pro Thr Cys His Asp Asp Val Val Lys Ile Val Asn Leu  
 210 215 220

Ala Cys Lys Tyr Asn Leu Cys Ile Ile Pro Ile Gly Gly Gly Thr Ser  
 225 230 235 240

Val Ser Tyr Gly Leu Met Cys Pro Ala Asp Glu Thr Arg Thr Ile Ile  
 245 250 255

Ser Leu Asp Thr Ser Gln Met Asn Arg Ile Leu Trp Val Asp Glu Asn  
 260 265 270

Asn Leu Thr Ala His Val Glu Ala Gly Ile Thr Gly Gln Glu Leu Glu  
 275 280 285

Arg Gln Leu Lys Glu Ser Gly Tyr Cys Thr Gly His Glu Pro Asp Ser  
 290 295 300

Leu Glu Phe Ser Thr Val Gly Gly Trp Val Ser Thr Arg Ala Ser Gly  
 305 310 315 320

Met Lys Lys Asn Ile Tyr Gly Asn Ile Glu Asp Leu Val Val His Ile  
 325 330 335

Lys Met Val Thr Pro Arg Gly Ile Ile Glu Lys Ser Cys Gln Gly Pro  
 340 345 350

Arg Met Ser Thr Gly Pro Asp Ile His His Phe Ile Met Gly Ser Glu  
 355 360 365

Gly Thr Leu Gly Val Ile Thr Glu Ala Thr Ile Lys Ile Arg Pro Val  
 370 375 380

Pro Glu Tyr Gln Lys Tyr Gly Ser Val Ala Phe Pro Asn Phe Glu Gln  
 385 390 395 400

Gly Val Ala Cys Leu Arg Glu Ile Ala Lys Gln Arg Cys Ala Pro Ala  
 405 410 415

Ser Ile Arg Leu Met Asp Asn Lys Gln Phe Gln Phe Gly His Ala Leu  
 420 425 430

Lys Pro Gln Val Ser Ser Ile Phe Thr Ser Phe Leu Asp Gly Leu Lys  
 435 440 445

Lys Phe Tyr Ile Thr Lys Phe Lys Gly Phe Asp Pro Asn Gln Leu Ser  
 450 455 460

Val Ala Thr Leu Leu Phe Glu Gly Asp Arg Glu Lys Val Leu Gln His  
 465 470 475 480

Glu Lys Gln Val Tyr Asp Ile Ala Ala Lys Phe Gly Gly Leu Ala Ala

485

490

495

Gly Glu Asp Asn Gly Gln Arg Gly Tyr Leu Leu Thr Tyr Val Ile Ala  
                   500                                  505                                  510

Tyr Ile Arg Asp Leu Ala Leu Glu Tyr Tyr Val Leu Gly Glu Ser Phe  
                   515                                  520                                  525

Glu Thr Ser Ala Pro Trp Asp Arg Val Val Asp Leu Cys Arg Asn Val  
                   530                                  535                                  540

Lys Glu Arg Ile Thr Arg Glu Cys Lys Glu Lys Gly Val Gln Phe Ala  
                   545                                  550                                  555                                  560

Pro Phe Ser Thr Cys Arg Val Thr Gln Thr Tyr Asp Ala Gly Ala Cys  
                                   565                                  570                                  575

Ile Tyr Phe Tyr Phe Ala Phe Asn Tyr Arg Gly Ile Ser Asp Pro Leu  
                                   580                                  585                                  590

Thr Val Phe Glu Gln Thr Glu Ala Ala Ala Arg Glu Glu Ile Leu Ala  
                   595                                  600                                  605

Asn Gly Gly Ser Leu Ser His His His Gly Val Gly Lys Leu Arg Lys  
                   610                                  615                                  620

Gln Trp Leu Lys Glu Ser Ile Ser Asp Val Gly Phe Gly Met Leu Lys  
                   625                                  630                                  635                                  640

Ser Val Lys Glu Tyr Val Asp Pro Asn Asn Ile Phe Gly Asn Arg Asn  
                                   645                                  650                                  655

Leu Leu

<210> 164  
 <211> 482  
 <212> PRT  
 <213> Homo sapiens

<400> 164

Met Pro Pro Ser Pro Leu Asp Asp Arg Val Val Val Ala Leu Ser Arg  
   1                  5                                  10                                  15

Pro Val Arg Pro Gln Asp Leu Asn Leu Cys Leu Asp Ser Ser Tyr Leu  
20 25 30

Gly Ser Ala Asn Pro Gly Ser Asn Ser His Pro Pro Val Ile Ala Thr  
35 40 45

Thr Val Val Ser Leu Lys Ala Ala Asn Leu Thr Tyr Met Pro Ser Ser  
50 55 60

Ser Gly Ser Ala Arg Ser Leu Asn Cys Gly Cys Ser Ser Ala Ser Cys  
65 70 75 80

Cys Thr Val Ala Thr Tyr Asp Lys Asp Asn Gln Ala Gln Thr Gln Ala  
85 90 95

Ile Ala Ala Gly Thr Thr Thr Thr Ala Ile Gly Thr Ser Thr Thr Cys  
100 105 110

Pro Ala Asn Gln Met Val Asn Asn Asn Glu Asn Thr Gly Ser Leu Ser  
115 120 125

Pro Ser Ser Gly Val Gly Ser Pro Val Ser Gly Thr Pro Lys Gln Leu  
130 135 140

Ala Ser Ile Lys Ile Ile Tyr Pro Asn Asp Leu Ala Lys Lys Met Thr  
145 150 155 160

Lys Cys Ser Lys Ser His Leu Pro Ser Gln Gly Pro Val Ile Ile Asp  
165 170 175

Cys Arg Pro Phe Met Glu Tyr Asn Lys Ser His Ile Gln Gly Ala Val  
180 185 190

His Ile Asn Cys Ala Asp Lys Ile Ser Arg Arg Arg Leu Gln Gln Gly  
195 200 205

Lys Ile Thr Val Leu Asp Leu Ile Ser Cys Arg Glu Gly Lys Asp Ser  
210 215 220

Phe Lys Arg Ile Phe Ser Lys Glu Ile Ile Val Tyr Asp Glu Asn Thr  
225 230 235 240

Asn Glu Pro Ser Arg Val Met Pro Ser Gln Pro Leu His Ile Val Leu  
 245 250 255  
 Glu Ser Leu Lys Arg Glu Gly Lys Glu Pro Leu Val Leu Lys Gly Gly  
 260 265 270  
 Leu Ser Ser Phe Lys Gln Asn His Glu Asn Leu Cys Asp Asn Ser Leu  
 275 280 285  
 Gln Leu Gln Glu Cys Arg Glu Val Gly Gly Gly Ala Ser Ala Ala Ser  
 290 295 300  
 Ser Leu Leu Pro Gln Pro Ile Pro Thr Thr Pro Asp Ile Glu Asn Ala  
 305 310 315 320  
 Glu Leu Thr Pro Ile Leu Pro Phe Leu Phe Leu Gly Asn Glu Gln Asp  
 325 330 335  
 Ala Gln Asp Leu Asp Thr Met Gln Arg Leu Asn Ile Gly Tyr Val Ile  
 340 345 350  
 Asn Val Thr Thr His Leu Pro Leu Tyr His Tyr Glu Lys Gly Leu Phe  
 355 360 365  
 Asn Tyr Lys Arg Leu Pro Ala Thr Asp Ser Asn Lys Gln Asn Leu Arg  
 370 375 380  
 Gln Tyr Phe Glu Glu Ala Phe Glu Phe Ile Glu Glu Ala His Gln Cys  
 385 390 395 400  
 Gly Lys Gly Leu Leu Ile His Cys Gln Ala Gly Val Ser Arg Ser Ala  
 405 410 415  
 Thr Ile Val Ile Ala Tyr Leu Met Lys His Thr Arg Met Thr Met Thr  
 420 425 430  
 Asp Ala Tyr Lys Phe Val Lys Gly Lys Arg Pro Ile Ile Ser Pro Asn  
 435 440 445  
 Leu Asn Phe Met Gly Gln Leu Leu Glu Phe Glu Glu Asp Leu Asn Asn  
 450 455 460  
 Gly Val Thr Pro Arg Ile Leu Thr Pro Lys Leu Met Gly Val Glu Thr

465                                      470                                      475                                      480

Val Val

<210> 165  
 <211> 407  
 <212> PRT  
 <213> Homo sapiens

<400> 165

Met Glu Ser Ala Ile Thr Leu Trp Gln Phe Leu Leu Gln Leu Leu Leu  
 1                                      5                                      10                                      15

Asp Gln Lys His Glu His Leu Ile Cys Trp Thr Ser Asn Asp Gly Glu  
                                     20                                      25                                      30

Phe Lys Leu Leu Lys Ala Glu Glu Val Ala Lys Leu Trp Gly Leu Arg  
                                     35                                      40                                      45

Lys Asn Lys Thr Asn Met Asn Tyr Asp Lys Leu Ser Arg Ala Leu Arg  
                                     50                                      55                                      60

Tyr Tyr Tyr Asp Lys Asn Ile Ile Lys Lys Val Ile Gly Gln Lys Phe  
 65                                      70                                      75                                      80

Val Tyr Lys Phe Val Ser Phe Pro Glu Ile Leu Lys Met Asp Pro His  
                                     85                                      90                                      95

Ala Val Glu Ile Ser Arg Glu Ser Leu Leu Leu Gln Asp Ser Asp Cys  
                                     100                                      105                                      110

Lys Val Ser Pro Glu Gly Arg Glu Ala His Lys His Gly Leu Ala Val  
                                     115                                      120                                      125

Leu Arg Ser Thr Ser Arg Asn Glu Tyr Ile His Ser Gly Leu Tyr Ser  
                                     130                                      135                                      140

Ser Phe Thr Ile Asn Ser Leu Glu Asn Pro Pro Asp Ala Phe Lys Ala  
 145                                      150                                      155                                      160

Ile Lys Arg Glu Lys Leu Glu Glu Pro Pro Glu Asp Ser Pro Pro Val  
                                     165                                      170                                      175

Glu Glu Val Arg Thr Val Ile Arg Phe Val Thr Asn Lys Thr Asp Lys  
 180 185 190

His Val Thr Arg Pro Val Val Ser Leu Pro Ser Thr Ser Glu Ala Ala  
 195 200 205

Ala Ala Ser Ala Phe Leu Ala Ser Ser Val Ser Ala Lys Ile Ser Ser  
 210 215 220

Leu Met Leu Pro Asn Ala Ala Ser Ile Ser Ser Ala Ser Pro Phe Ser  
 225 230 235 240

Ser Arg Ser Pro Ser Leu Ser Pro Lys Ser Pro Leu Pro Ser Glu His  
 245 250 255

Arg Ser Leu Phe Leu Glu Ala Ala Cys His Asp Ser Asp Ser Leu Glu  
 260 265 270

Pro Leu Asn Leu Ser Ser Gly Ser Lys Thr Lys Ser Pro Ser Leu Pro  
 275 280 285

Pro Lys Ala Lys Lys Pro Lys Gly Leu Glu Ile Ser Ala Pro Pro Leu  
 290 295 300

Val Leu Ser Gly Thr Asp Ile Gly Ser Ile Ala Leu Asn Ser Pro Ala  
 305 310 315 320

Leu Pro Ser Gly Ser Leu Thr Pro Ala Phe Phe Thr Ala Gln Thr Pro  
 325 330 335

Asn Gly Leu Leu Leu Thr Pro Ser Pro Leu Leu Ser Ser Ile His Phe  
 340 345 350

Trp Ser Ser Leu Ser Pro Val Ala Pro Leu Ser Pro Ala Arg Leu Gln  
 355 360 365

Gly Pro Ser Thr Leu Phe Gln Phe Pro Thr Leu Leu Asn Gly His Met  
 370 375 380

Pro Val Pro Ile Pro Ser Leu Asp Arg Ala Ala Ser Pro Val Leu Leu  
 385 390 395 400



Ser Ser Asn Ser Gln Lys Ser  
405

<210> 166  
<211> 364  
<212> PRT  
<213> Homo sapiens

<400> 166

Met Ala Ala Ile Ser Thr Ser Ile Pro Val Ile Ser Gln Pro Gln Phe  
1 5 10 15

Thr Ala Met Asn Glu Pro Gln Cys Phe Tyr Asn Glu Ser Ile Ala Phe  
20 25 30

Phe Tyr Asn Arg Ser Gly Lys His Leu Ala Thr Glu Trp Asn Thr Val  
35 40 45

Ser Lys Leu Val Met Gly Leu Gly Ile Thr Val Cys Ile Phe Ile Met  
50 55 60

Leu Ala Asn Leu Leu Val Met Val Ala Ile Tyr Val Asn Arg Arg Phe  
65 70 75 80

His Phe Pro Ile Tyr Tyr Leu Met Ala Asn Leu Ala Ala Ala Asp Phe  
85 90 95

Phe Ala Gly Leu Ala Tyr Phe Tyr Leu Met Phe Asn Thr Gly Pro Asn  
100 105 110

Thr Arg Arg Leu Thr Val Ser Thr Trp Leu Leu Arg Gln Gly Leu Ile  
115 120 125

Asp Thr Ser Leu Thr Ala Ser Val Ala Asn Leu Leu Ala Ile Ala Ile  
130 135 140

Glu Arg His Ile Thr Val Phe Arg Met Gln Leu His Thr Arg Met Ser  
145 150 155 160

Asn Arg Arg Val Val Val Val Ile Val Val Ile Trp Thr Met Ala Ile  
165 170 175

Val Met Gly Ala Ile Pro Ser Val Gly Trp Asn Cys Ile Cys Asp Ile  
180 185 190

Glu Asn Cys Ser Asn Met Ala Pro Leu Tyr Ser Asp Ser Tyr Leu Val  
 195 200 205

Phe Trp Ala Ile Phe Asn Leu Val Thr Phe Val Val Met Val Val Leu  
 210 215 220

Tyr Ala His Ile Phe Gly Tyr Val Arg Gln Arg Thr Met Arg Met Ser  
 225 230 235 240

Arg His Ser Ser Gly Pro Arg Arg Asn Arg Asp Thr Met Met Ser Leu  
 245 250 255

Leu Lys Thr Val Val Ile Val Leu Gly Ala Phe Ile Ile Cys Trp Thr  
 260 265 270

Pro Gly Leu Val Leu Leu Leu Leu Asp Val Cys Cys Pro Gln Cys Asp  
 275 280 285

Val Leu Ala Tyr Glu Lys Phe Phe Leu Leu Leu Ala Glu Phe Asn Ser  
 290 295 300

Ala Met Asn Pro Ile Ile Tyr Ser Tyr Arg Asp Lys Glu Met Ser Ala  
 305 310 315 320

Thr Phe Arg Gln Ile Leu Cys Cys Gln Arg Ser Glu Asn Pro Thr Gly  
 325 330 335

Pro Thr Glu Gly Ser Asp Arg Ser Ala Ser Ser Leu Asn His Thr Ile  
 340 345 350

Leu Ala Gly Val His Ser Asn Asp His Ser Val Val  
 355 360

<210> 167  
 <211> 759  
 <212> PRT  
 <213> Homo sapiens

<400> 167

Met Glu Ser Ser Pro Phe Asn Arg Arg Gln Trp Thr Ser Leu Ser Leu  
 1 5 10 15

Arg Val Thr Ala Lys Glu Leu Ser Leu Val Asn Lys Asn Lys Ser Ser  
 20 25 30

Ala Ile Val Glu Ile Phe Ser Lys Tyr Gln Lys Ala Ala Glu Glu Thr  
 35 40 45

Asn Met Glu Lys Lys Arg Ser Asn Thr Glu Asn Leu Ser Gln His Phe  
 50 55 60

Arg Lys Gly Thr Leu Thr Val Leu Lys Lys Lys Trp Glu Asn Pro Gly  
 65 70 75 80

Leu Gly Ala Glu Ser His Thr Asp Ser Leu Arg Asn Ser Ser Thr Glu  
 85 90 95

Ile Arg His Arg Ala Asp His Pro Pro Ala Glu Val Thr Ser His Ala  
 100 105 110

Ala Ser Gly Ala Lys Ala Asp Gln Glu Glu Gln Ile His Pro Arg Ser  
 115 120 125

Arg Leu Arg Ser Pro Pro Glu Ala Leu Val Gln Gly Arg Tyr Pro His  
 130 135 140

Ile Lys Asp Gly Glu Asp Leu Lys Asp His Ser Thr Glu Ser Lys Lys  
 145 150 155 160

Met Glu Asn Cys Leu Gly Glu Ser Arg His Glu Val Glu Lys Ser Glu  
 165 170 175

Ile Ser Glu Asn Thr Asp Ala Ser Gly Lys Ile Glu Lys Tyr Asn Val  
 180 185 190

Pro Leu Asn Arg Leu Lys Met Met Phe Glu Lys Gly Glu Pro Thr Gln  
 195 200 205

Thr Lys Ile Leu Arg Ala Gln Ser Arg Ser Ala Ser Gly Arg Lys Ile  
 210 215 220

Ser Glu Asn Ser Tyr Ser Leu Asp Asp Leu Glu Ile Gly Pro Gly Gln  
 225 230 235 240

Leu Ser Ser Ser Thr Phe Asp Ser Glu Lys Asn Glu Ser Arg Arg Asn

245	250	255
Leu Glu Leu Pro Arg Leu Ser Glu Thr Ser Ile Lys Asp Arg Met Ala		
260	265	270
Lys Tyr Gln Ala Ala Val Ser Lys Gln Ser Ser Ser Thr Asn Tyr Thr		
275	280	285
Asn Glu Leu Lys Ala Ser Gly Gly Glu Ile Lys Ile His Lys Met Glu		
290	295	300
Gln Lys Glu Asn Val Pro Pro Gly Pro Glu Val Cys Ile Thr His Gln		
305	310	315
Glu Gly Glu Lys Ile Ser Ala Asn Glu Asn Ser Leu Ala Val Arg Ser		
325	330	335
Thr Pro Ala Glu Asp Asp Ser Arg Asp Ser Gln Val Lys Ser Glu Val		
340	345	350
Gln Gln Pro Val His Pro Lys Pro Leu Ser Pro Asp Ser Arg Ala Ser		
355	360	365
Ser Leu Ser Glu Ser Ser Pro Pro Lys Ala Met Lys Lys Phe Gln Ala		
370	375	380
Pro Ala Arg Glu Thr Cys Val Glu Cys Gln Lys Thr Val Tyr Pro Met		
385	390	395
Glu Arg Leu Leu Ala Asn Gln Gln Val Phe His Ile Ser Cys Phe Arg		
405	410	415
Cys Ser Tyr Cys Asn Asn Lys Leu Ser Leu Gly Thr Tyr Ala Ser Leu		
420	425	430
His Gly Arg Ile Tyr Cys Lys Pro His Phe Asn Gln Leu Phe Lys Ser		
435	440	445
Lys Gly Asn Tyr Asp Glu Gly Phe Gly His Arg Pro His Lys Asp Leu		
450	455	460
Trp Ala Ser Lys Asn Glu Asn Glu Glu Ile Leu Glu Arg Pro Ala Gln		
465	470	475
		480

Leu Ala Asn Ala Arg Glu Thr Pro His Ser Pro Gly Val Glu Asp Ala  
 485 490 495

Pro Ile Ala Lys Val Gly Val Leu Ala Ala Ser Met Glu Ala Lys Ala  
 500 505 510

Ser Ser Gln Gln Glu Lys Glu Asp Lys Pro Ala Glu Thr Lys Lys Leu  
 515 520 525

Arg Ile Ala Trp Pro Pro Pro Thr Glu Leu Gly Ser Ser Gly Ser Ala  
 530 535 540

Leu Glu Glu Gly Ile Lys Met Ser Lys Pro Lys Trp Pro Pro Glu Asp  
 545 550 555 560

Glu Ile Ser Lys Pro Glu Val Pro Glu Asp Val Asp Leu Asp Leu Lys  
 565 570 575

Lys Leu Arg Arg Ser Ser Ser Leu Lys Glu Arg Ser Arg Pro Phe Thr  
 580 585 590

Val Ala Ala Ser Phe Gln Ser Thr Ser Val Lys Ser Pro Lys Thr Val  
 595 600 605

Ser Pro Pro Ile Arg Lys Gly Trp Ser Met Ser Glu Gln Ser Glu Glu  
 610 615 620

Ser Val Gly Gly Arg Val Ala Glu Arg Lys Gln Val Glu Asn Ala Lys  
 625 630 635 640

Ala Ser Lys Lys Asn Gly Asn Val Gly Lys Thr Thr Trp Gln Asn Lys  
 645 650 655

Glu Ser Lys Gly Glu Thr Gly Lys Arg Ser Lys Glu Gly His Ser Leu  
 660 665 670

Glu Met Glu Asn Glu Asn Leu Val Glu Asn Gly Ala Asp Ser Asp Glu  
 675 680 685

Asp Asp Asn Ser Phe Leu Lys Gln Gln Ser Pro Gln Glu Pro Lys Ser  
 690 695 700

Leu Asn Trp Ser Ser Phe Val Asp Asn Thr Phe Ala Glu Glu Phe Thr  
705 710 715 720

Thr Gln Asn Gln Lys Ser Gln Asp Val Glu Leu Trp Glu Gly Glu Val  
725 730 735

Val Lys Glu Leu Ser Val Glu Glu Gln Ile Lys Arg Asn Arg Tyr Tyr  
740 745 750

Asp Glu Asp Glu Asp Glu Glu  
755

<210> 168  
<211> 695  
<212> PRT  
<213> Homo sapiens

<400> 168

Met Ile Met Lys Ser Asn Phe Asp Glu Thr Tyr Ile Glu Asn Val Val  
1 5 10 15

Arg Asn Ile Leu Lys Gly Gln Asp Val Asp Ser Lys Glu Ala Gln Leu  
20 25 30

Ile Ser Phe Leu Ala Leu Leu Ser Ser Tyr Val Thr Asp Ser Thr Ile  
35 40 45

Ser Val Ser Gln Cys Glu Ile Phe Leu Gly Ile Ile Tyr Thr Ser Thr  
50 55 60

Pro Trp Glu Pro Glu Ser Leu Glu Asp Lys Met Gly Thr Tyr Ser Thr  
65 70 75 80

Leu Leu Ile Lys Thr Glu Val Ala Glu Tyr Gly Arg Tyr Thr Gly Val  
85 90 95

Arg Ile Ile His Pro Leu Ile Ala Leu Tyr Cys Leu Lys Glu Leu Glu  
100 105 110

Arg Ser Tyr His Leu Asp Lys Cys Gln Ile Ala Leu Asn Ile Leu Glu  
115 120 125

Glu Asn Leu Phe Tyr Asp Ser Gly Ile Gly Arg Asp Lys Phe Gln His

130

135

140

Asp Val Gln Thr Leu Leu Leu Thr Arg Gln Arg Lys Val Tyr Gly Asp  
 145 150 155 160

Glu Thr Asp Thr Leu Phe Ser Pro Leu Met Glu Ala Leu Gln Asn Lys  
 165 170 175

Asp Ile Glu Lys Val Leu Ser Ala Gly Ser Arg Arg Phe Pro Gln Asn  
 180 185 190

Ala Phe Ile Cys Gln Ala Leu Ala Arg His Phe Tyr Ile Lys Glu Lys  
 195 200 205

Asp Phe Asn Thr Ala Leu Asp Trp Ala Arg Gln Ala Lys Met Lys Ala  
 210 215 220

Pro Lys Asn Ser Tyr Ile Ser Asp Thr Leu Gly Gln Val Tyr Lys Ser  
 225 230 235 240

Glu Ile Lys Trp Trp Leu Asp Gly Asn Lys Asn Cys Arg Ser Ile Thr  
 245 250 255

Val Asn Asp Leu Thr His Leu Leu Glu Ala Ala Glu Lys Ala Ser Arg  
 260 265 270

Ala Phe Lys Glu Ser Gln Arg Gln Thr Asp Ser Lys Asn Tyr Glu Thr  
 275 280 285

Glu Asn Trp Ser Pro Gln Lys Ser Gln Arg Arg Tyr Asp Met Tyr Asn  
 290 295 300

Thr Ala Cys Phe Leu Gly Glu Ile Glu Val Gly Leu Tyr Thr Ile Gln  
 305 310 315 320

Ile Leu Gln Leu Thr Pro Phe Phe His Lys Glu Asn Glu Leu Ser Lys  
 325 330 335

Lys His Met Val Gln Phe Leu Ser Gly Lys Trp Thr Ile Pro Pro Asp  
 340 345 350

Pro Arg Asn Glu Cys Tyr Leu Ala Leu Ser Lys Phe Thr Ser His Leu  
 355 360 365

Lys Asn Leu Gln Ser Asp Leu Lys Arg Cys Phe Asp Phe Phe Ile Asp  
 370 375 380

Tyr Met Val Leu Leu Lys Met Arg Tyr Thr Gln Lys Glu Ile Ala Glu  
 385 390 395 400

Ile Met Leu Ser Lys Lys Val Ser Arg Cys Phe Arg Lys Tyr Thr Glu  
 405 410 415

Leu Phe Cys His Leu Asp Pro Cys Leu Leu Gln Ser Lys Glu Ser Gln  
 420 425 430

Leu Leu Gln Glu Glu Asn Cys Arg Lys Lys Leu Glu Ala Leu Arg Ala  
 435 440 445

Asp Arg Phe Ala Gly Leu Leu Glu Tyr Leu Asn Pro Asn Tyr Lys Asp  
 450 455 460

Ala Thr Thr Met Glu Ser Ile Val Asn Glu Tyr Ala Phe Leu Leu Gln  
 465 470 475 480

Gln Asn Ser Lys Lys Pro Met Thr Asn Glu Lys Gln Asn Ser Ile Leu  
 485 490 495

Ala Asn Ile Ile Leu Ser Cys Leu Lys Pro Asn Ser Lys Leu Ile Gln  
 500 505 510

Pro Leu Thr Thr Leu Lys Lys Gln Leu Arg Glu Val Leu Gln Phe Val  
 515 520 525

Gly Leu Ser His Gln Tyr Pro Gly Pro Tyr Phe Leu Ala Cys Leu Leu  
 530 535 540

Phe Trp Pro Glu Asn Gln Glu Leu Asp Gln Asp Ser Lys Leu Ile Glu  
 545 550 555 560

Lys Tyr Val Ser Ser Leu Asn Arg Ser Phe Arg Gly Gln Tyr Lys Arg  
 565 570 575

Met Cys Arg Ser Lys Gln Ala Ser Thr Leu Phe Tyr Leu Gly Lys Arg  
 580 585 590



Lys Gly Leu Asn Ser Ile Val His Lys Ala Lys Ile Glu Gln Tyr Phe  
 595 600 605

Asp Lys Ala Gln Asn Thr Asn Ser Leu Trp His Ser Gly Asp Val Trp  
 610 615 620

Lys Lys Asn Glu Val Lys Asp Leu Leu Arg Arg Leu Thr Gly Gln Ala  
 625 630 635 640

Glu Gly Lys Leu Ile Ser Val Glu Tyr Gly Thr Glu Glu Lys Ile Lys  
 645 650 655

Ile Pro Val Ile Ser Val Tyr Ser Gly Pro Leu Arg Ser Gly Arg Asn  
 660 665 670

Ile Glu Arg Val Ser Phe Tyr Leu Gly Phe Ser Ile Glu Gly Pro Leu  
 675 680 685

Ala Tyr Asp Ile Glu Val Ile  
 690 695

<210> 169  
 <211> 746  
 <212> PRT  
 <213> Homo sapiens

<400> 169

Met Gln Ala Lys Lys Arg Tyr Phe Ile Leu Leu Ser Ala Gly Ser Cys  
 1 5 10 15

Leu Ala Leu Leu Phe Tyr Phe Gly Gly Leu Gln Phe Arg Ala Ser Arg  
 20 25 30

Ser His Ser Arg Arg Glu Glu His Ser Gly Arg Asn Gly Leu His His  
 35 40 45

Pro Ser Pro Asp His Phe Trp Pro Arg Phe Pro Glu Pro Leu Arg Pro  
 50 55 60

Phe Val Pro Trp Asp Gln Leu Glu Asn Glu Asp Ser Ser Val His Ile  
 65 70 75 80

Ser Pro Arg Gln Lys Arg Asp Ala Asn Ser Ser Ile Tyr Lys Gly Lys

248

Lys Tyr Asp Tyr Arg Glu Met Leu His Asn Ala Thr Phe Cys Leu Val  
 325 330 335

Pro Arg Gly Arg Arg Leu Gly Ser Phe Arg Phe Leu Glu Ala Leu Gln  
 340 345 350

Ala Ala Cys Val Pro Val Met Leu Ser Asn Gly Trp Glu Leu Pro Phe  
 355 360 365

Ser Glu Val Ile Asn Trp Asn Gln Ala Ala Val Ile Gly Asp Glu Arg  
 370 375 380

Leu Leu Leu Gln Ile Pro Ser Thr Ile Arg Ser Ile His Gln Asp Lys  
 385 390 395 400

Ile Leu Ala Leu Arg Gln Gln Thr Gln Phe Leu Trp Glu Ala Tyr Phe  
 405 410 415

Ser Ser Val Glu Lys Ile Val Leu Thr Thr Leu Glu Ile Ile Gln Asp  
 420 425 430

Arg Ile Phe Lys His Ile Ser Arg Asn Ser Leu Ile Trp Asn Lys His  
 435 440 445

Pro Gly Gly Leu Phe Val Leu Pro Gln Tyr Ser Ser Tyr Leu Gly Asp  
 450 455 460

Phe Pro Tyr Tyr Tyr Ala Asn Leu Gly Leu Lys Pro Pro Ser Lys Phe  
 465 470 475 480

Thr Ala Val Ile His Ala Val Thr Pro Leu Val Ser Gln Ser Gln Pro  
 485 490 495

Val Leu Lys Leu Leu Val Ala Ala Ala Lys Ser Gln Tyr Cys Ala Gln  
 500 505 510

Ile Ile Val Leu Trp Asn Cys Asp Lys Pro Leu Pro Ala Lys His Arg  
 515 520 525

Trp Pro Ala Thr Ala Val Pro Val Val Val Ile Glu Gly Glu Ser Lys  
 530 535 540

Val Met Ser Ser Arg Phe Leu Pro Tyr Asp Asn Ile Ile Thr Asp Ala  
 545 550 555 560

Val Leu Ser Leu Asp Glu Asp Thr Val Leu Ser Thr Thr Glu Val Asp  
 565 570 575

Phe Ala Phe Thr Val Trp Gln Ser Phe Pro Glu Arg Ile Val Gly Tyr  
 580 585 590

Pro Ala Arg Ser His Phe Trp Asp Asn Ser Lys Glu Arg Trp Gly Tyr  
 595 600 605

Thr Ser Lys Trp Thr Asn Asp Tyr Ser Met Val Leu Thr Gly Ala Ala  
 610 615 620

Ile Tyr His Lys Tyr Tyr His Tyr Leu Tyr Ser His Tyr Leu Pro Ala  
 625 630 635 640

Ser Leu Lys Asn Met Val Asp Gln Leu Ala Asn Cys Glu Asp Ile Leu  
 645 650 655

Met Asn Phe Leu Val Ser Ala Val Thr Lys Leu Pro Pro Ile Lys Val  
 660 665 670

Thr Gln Lys Lys Gln Tyr Lys Glu Thr Met Met Gly Gln Thr Ser Arg  
 675 680 685

Ala Ser Arg Trp Ala Asp Pro Asp His Phe Ala Gln Arg Gln Ser Cys  
 690 695 700

Met Asn Thr Phe Ala Ser Trp Phe Gly Tyr Met Pro Leu Ile His Ser  
 705 710 715 720

Gln Met Arg Leu Asp Pro Val Leu Phe Lys Asp Gln Val Ser Ile Leu  
 725 730 735

Arg Lys Lys Tyr Arg Asp Ile Glu Arg Leu  
 740 745

<210> 170  
 <211> 1069  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 170

Met Leu Arg Met Arg Thr Ala Gly Trp Ala Arg Gly Trp Cys Leu Gly  
 1 5 10 15

Cys Cys Leu Leu Leu Pro Leu Ser Phe Ser Leu Ala Ala Ala Lys Gln  
 20 25 30

Leu Leu Arg Tyr Arg Leu Ala Glu Glu Gly Pro Ala Asp Val Arg Ile  
 35 40 45

Gly Asn Val Ala Ser Asp Leu Gly Ile Val Thr Gly Ser Gly Glu Val  
 50 55 60

Thr Phe Ser Leu Glu Ser Gly Ser Glu Tyr Leu Lys Ile Asp Asn Leu  
 65 70 75 80

Thr Gly Glu Leu Ser Thr Ser Glu Arg Arg Ile Asp Arg Glu Lys Leu  
 85 90 95

Pro Gln Cys Gln Met Ile Phe Asp Glu Asn Glu Cys Phe Leu Asp Phe  
 100 105 110

Glu Val Ser Val Ile Gly Pro Ser Gln Ser Trp Val Asp Leu Phe Glu  
 115 120 125

Gly Gln Val Ile Val Leu Asp Ile Asn Asp Asn Thr Pro Thr Phe Pro  
 130 135 140

Ser Pro Val Leu Thr Leu Thr Val Glu Glu Asn Arg Pro Val Gly Thr  
 145 150 155 160

Leu Tyr Leu Leu Pro Thr Ala Thr Asp Arg Asp Phe Gly Arg Asn Gly  
 165 170 175

Ile Glu Arg Tyr Glu Leu Leu Gln Glu Pro Gly Gly Gly Gly Ser Gly  
 180 185 190

Gly Glu Ser Arg Arg Ala Gly Ala Ala Asp Ser Ala Pro Tyr Pro Gly  
 195 200 205

Gly Gly Gly Asn Gly Ala Ser Gly Gly Gly Ser Gly Gly Ser Lys Arg  
 210 215 220

Arg Leu Asp Ala Ser Glu Gly Gly Gly Gly Thr Asn Pro Gly Gly Arg  
225 230 235 240

Ser Ser Val Phe Glu Leu Gln Val Ala Asp Thr Pro Asp Gly Glu Lys  
245 250 255

Gln Pro Gln Leu Ile Val Lys Gly Ala Leu Asp Arg Glu Gln Arg Asp  
260 265 270

Ser Tyr Glu Leu Thr Leu Arg Val Arg Asp Gly Gly Asp Pro Pro Arg  
275 280 285

Ser Ser Gln Ala Ile Leu Arg Val Leu Ile Thr Asp Val Asn Asp Asn  
290 295 300

Ser Pro Arg Phe Glu Lys Ser Val Tyr Glu Ala Asp Leu Ala Glu Asn  
305 310 315 320

Ser Ala Pro Gly Thr Pro Ile Leu Gln Leu Arg Ala Ala Asp Leu Asp  
325 330 335

Val Gly Val Asn Gly Gln Ile Glu Tyr Val Phe Gly Ala Ala Thr Glu  
340 345 350

Ser Val Arg Arg Leu Leu Arg Leu Asp Glu Thr Ser Gly Trp Leu Ser  
355 360 365

Val Leu His Arg Ile Asp Arg Glu Glu Val Asn Gln Leu Arg Phe Thr  
370 375 380

Val Met Ala Arg Asp Arg Gly Gln Pro Pro Lys Thr Asp Lys Ala Thr  
385 390 395 400

Val Val Leu Asn Ile Lys Asp Glu Asn Asp Asn Val Pro Ser Ile Glu  
405 410 415

Ile Arg Lys Ile Gly Arg Ile Pro Leu Lys Asp Gly Val Ala Asn Val  
420 425 430

Ala Glu Asp Val Leu Val Asp Thr Pro Ile Ala Leu Val Gln Val Ser  
435 440 445

Asp Arg Asp Gln Gly Glu Asn Gly Val Val Thr Cys Thr Val Val Gly  
 450 455 460

Asp Val Pro Phe Gln Leu Lys Pro Ala Ser Asp Thr Glu Gly Asp Gln  
 465 470 475 480

Asn Lys Lys Lys Tyr Phe Leu His Thr Ser Thr Pro Leu Asp Tyr Glu  
 485 490 495

Ala Thr Arg Glu Phe Asn Val Val Ile Val Ala Val Asp Ser Gly Ser  
 500 505 510

Pro Ser Leu Ser Ser Lys Asn Ser Leu Ile Val Lys Val Gly Asp Thr  
 515 520 525

Asn Asp Asn Pro Pro Met Phe Gly Gln Ser Val Val Glu Val Tyr Phe  
 530 535 540

Pro Glu Asn Asn Ile Pro Gly Glu Arg Val Ala Thr Val Leu Ala Thr  
 545 550 555 560

Asp Ala Asp Ser Gly Lys Asn Ala Glu Ile Ala Tyr Ser Leu Asp Ser  
 565 570 575

Ser Val Met Gly Ile Phe Ala Ile Asp Pro Asp Ser Gly Asp Ile Leu  
 580 585 590

Val Asn Thr Val Leu Asp Arg Glu Gln Thr Asp Arg Tyr Glu Phe Lys  
 595 600 605

Val Asn Ala Lys Asp Lys Gly Ile Pro Val Leu Gln Gly Ser Thr Thr  
 610 615 620

Val Ile Val Gln Val Ala Asp Lys Asn Asp Asn Asp Pro Lys Phe Met  
 625 630 635 640

Gln Asp Val Phe Thr Phe Tyr Val Lys Glu Asn Leu Gln Pro Asn Ser  
 645 650 655

Pro Val Gly Met Val Thr Val Met Asp Ala Asp Lys Gly Arg Asn Ala  
 660 665 670

Glu Met Ser Leu Tyr Ile Glu Glu Asn Asn Asn Ile Phe Ser Ile Glu  
675 680 685

Asn Asp Thr Gly Thr Ile Tyr Ser Thr Met Ser Phe Asp Arg Glu His  
690 695 700

Gln Thr Thr Tyr Thr Phe Arg Val Lys Ala Val Asp Gly Gly Asp Pro  
705 710 715 720

Pro Arg Ser Ala Thr Ala Thr Val Ser Leu Phe Val Met Asp Glu Asn  
725 730 735

Asp Asn Ala Pro Thr Val Thr Leu Pro Lys Asn Ile Ser Tyr Thr Leu  
740 745 750

Leu Pro Pro Ser Ser Asn Val Arg Thr Val Val Ala Thr Val Leu Ala  
755 760 765

Thr Asp Ser Asp Asp Gly Ile Asn Ala Asp Leu Asn Tyr Ser Ile Val  
770 775 780

Gly Gly Asn Pro Phe Lys Leu Phe Glu Ile Asp Pro Thr Ser Gly Val  
785 790 795 800

Val Ser Leu Val Gly Lys Leu Thr Gln Lys His Tyr Gly Leu His Arg  
805 810 815

Leu Val Val Gln Val Asn Asp Ser Gly Gln Pro Ser Gln Ser Thr Thr  
820 825 830

Thr Val Val His Val Phe Val Asn Glu Ser Val Ser Asn Ala Thr Ala  
835 840 845

Ile Asp Ser Gln Ile Ala Arg Ser Leu His Ile Pro Leu Thr Gln Asp  
850 855 860

Ile Ala Gly Asp Pro Ser Tyr Glu Ile Ser Lys Gln Arg Leu Ser Ile  
865 870 875 880

Val Ile Gly Val Val Ala Gly Ile Met Thr Val Ile Leu Ile Ile Leu  
885 890 895

Ile Val Val Met Ala Arg Tyr Cys Arg Ser Lys Asn Lys Asn Gly Tyr



Gly

<400> 171

255

Leu Leu Phe Leu Ser Ser Thr Cys Val Ala Tyr Val Ala Thr Arg Asp  
 20 25 30

Asn Cys Cys Ile Leu Asp Glu Arg Phe Gly Ser Tyr Cys Pro Thr Thr  
 35 40 45

Cys Gly Ile Ala Asp Phe Leu Ser Thr Tyr Gln Thr Lys Val Asp Lys  
 50 55 60

Asp Leu Gln Ser Leu Glu Asp Ile Leu His Gln Val Glu Asn Lys Thr  
 65 70 75 80

Ser Glu Val Lys Gln Leu Ile Lys Ala Ile Gln Leu Thr Tyr Asn Pro  
 85 90 95

Asp Glu Ser Ser Lys Pro Asn Met Ile Asp Ala Ala Thr Leu Lys Ser  
 100 105 110

Arg Lys Met Leu Glu Glu Ile Met Lys Tyr Glu Ala Ser Ile Leu Thr  
 115 120 125

His Asp Ser Ser Ile Arg Tyr Leu Gln Glu Ile Tyr Asn Ser Asn Asn  
 130 135 140

Gln Lys Ile Val Asn Leu Lys Glu Lys Val Ala Gln Leu Glu Ala Gln  
 145 150 155 160

Cys Gln Glu Pro Cys Lys Asp Thr Val Gln Ile His Asp Ile Thr Gly  
 165 170 175

Lys Asp Cys Gln Asp Ile Ala Asn Lys Gly Ala Lys Gln Ser Gly Leu  
 180 185 190

Tyr Phe Ile Lys Pro Leu Lys Ala Asn Gln Gln Phe Leu Val Tyr Cys  
 195 200 205

Glu Ile Asp Gly Ser Gly Asn Gly Trp Thr Val Phe Gln Lys Arg Leu  
 210 215 220

Asp Gly Ser Val Asp Phe Lys Lys Asn Trp Ile Gln Tyr Lys Glu Gly  
 225 230 235 240

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<210> 172
<211> 642
<212> PRT
<213> Homo sapiens
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&lt;400&gt; 172

Met Lys Arg Ser Ser Val Ser Ser Gly Gly Ala Gly Arg Leu Ser Met  
 1 5 10 15

Gln Glu Leu Arg Ser Gln Asp Val Asn Lys Gln Gly Leu Tyr Thr Pro  
 20 25 30

Gln Thr Lys Glu Lys Pro Thr Phe Gly Lys Leu Ser Ile Asn Lys Pro  
 35 40 45

Thr Ser Glu Arg Lys Val Ser Leu Phe Gly Lys Arg Thr Ser Gly His  
 50 55 60

Gly Ser Arg Asn Ser Gln Leu Gly Ile Phe Ser Ser Ser Glu Lys Ile  
 65 70 75 80

Lys Asp Pro Arg Pro Leu Asn Asp Lys Ala Phe Ile Gln Gln Cys Ile  
 85 90 95

Arg Gln Leu Cys Glu Phe Leu Thr Glu Asn Gly Tyr Ala His Asn Val  
 100 105 110

Ser Met Lys Ser Leu Gln Ala Pro Ser Val Lys Asp Phe Leu Lys Ile  
 115 120 125

Phe Thr Phe Leu Tyr Gly Phe Leu Cys Pro Ser Tyr Glu Leu Pro Asp  
 130 135 140

Thr Lys Phe Glu Glu Glu Val Pro Arg Ile Phe Lys Asp Leu Gly Tyr  
 145 150 155 160

Pro Phe Ala Leu Ser Lys Ser Ser Met Tyr Thr Val Gly Ala Pro His  
 165 170 175

Thr Trp Pro His Ile Val Ala Ala Leu Val Trp Leu Ile Asp Cys Ile  
 180 185 190

Lys Ile His Thr Ala Met Lys Glu Ser Ser Pro Leu Phe Asp Asp Gly  
 195 200 205

Gln Pro Trp Gly Glu Glu Thr Glu Asp Gly Ile Met His Asn Lys Leu  
 210 215 220

Phe Leu Asp Tyr Thr Ile Lys Cys Tyr Glu Ser Phe Met Ser Gly Ala  
 225 230 235 240

Asp Ser Phe Asp Glu Met Asn Ala Glu Leu Gln Ser Lys Leu Lys Asp  
 245 250 255

Leu Phe Asn Val Asp Ala Phe Lys Leu Glu Ser Leu Glu Ala Lys Asn  
 260 265 270

Arg Ala Leu Asn Glu Gln Ile Ala Arg Leu Glu Gln Glu Arg Glu Lys  
 275 280 285

Glu Pro Asn Arg Leu Glu Ser Leu Arg Lys Leu Lys Ala Ser Leu Gln  
 290 295 300

Gly Asp Val Gln Lys Tyr Gln Ala Tyr Met Ser Asn Leu Glu Ser His  
 305 310 315 320

Ser Ala Ile Leu Asp Gln Lys Leu Asn Gly Leu Asn Glu Glu Ile Ala  
 325 330 335

Arg Val Glu Leu Glu Cys Glu Thr Ile Lys Gln Glu Asn Thr Arg Leu  
 340 345 350

Gln Asn Ile Ile Asp Asn Gln Lys Tyr Ser Val Ala Asp Ile Glu Arg  
 355 360 365

Ile Asn His Glu Arg Asn Glu Leu Gln Gln Thr Ile Asn Lys Leu Thr  
 370 375 380

Lys Asp Leu Glu Ala Glu Gln Gln Lys Leu Trp Asn Glu Glu Leu Lys  
 385 390 395 400

Tyr Ala Arg Gly Lys Glu Ala Ile Glu Thr Gln Leu Ala Glu Tyr His  
 405 410 415

Lys Leu Ala Arg Lys Leu Lys Leu Ile Pro Lys Gly Ala Glu Asn Ser  
 420 425 430

Lys Gly Tyr Asp Phe Glu Ile Lys Phe Asn Pro Glu Ala Gly Ala Asn  
 435 440 445

Cys Leu Val Lys Tyr Arg Ala Gln Val Tyr Val Pro Leu Lys Glu Leu  
 450 455 460

Leu Asn Glu Thr Glu Glu Glu Ile Asn Lys Ala Leu Asn Lys Lys Met  
 465 470 475 480

Gly Leu Glu Asp Thr Leu Glu Gln Leu Asn Ala Met Ile Thr Glu Ser  
 485 490 495

Lys Arg Ser Val Arg Thr Leu Lys Glu Glu Val Gln Lys Leu Asp Asp  
 500 505 510

Leu Tyr Gln Gln Lys Ile Lys Glu Ala Glu Glu Glu Asp Glu Lys Cys  
 515 520 525

Ala Ser Glu Leu Glu Ser Leu Glu Lys His Lys His Leu Leu Glu Ser  
 530 535 540

Thr Val Asn Gln Gly Leu Ser Glu Ala Met Asn Glu Leu Asp Ala Val  
 545 550 555 560

Gln Arg Glu Tyr Gln Leu Val Val Gln Thr Thr Thr Glu Glu Arg Arg  
 565 570 575

Lys Val Gly Asn Asn Leu Gln Arg Leu Leu Glu Met Val Ala Thr His  
 580 585 590

Val Gly Ser Val Glu Lys His Leu Glu Glu Gln Ile Ala Lys Val Asp  
 595 600 605

Arg Glu Tyr Glu Glu Cys Met Ser Glu Asp Leu Ser Glu Asn Ile Lys  
 610 615 620

Glu Ile Arg Asp Lys Tyr Glu Lys Lys Ala Thr Leu Ile Lys Ser Ser  
 625 630 635 640

Glu Glu

<210> 173  
 <211> 178  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 173

Met Ser Pro Ser Gly Arg Leu Cys Leu Leu Thr Ile Val Gly Leu Ile  
 1 5 10 15

Leu Pro Thr Arg Gly Gln Thr Leu Lys Asp Thr Thr Ser Ser Ser Ser  
 20 25 30

Ala Asp Ser Thr Ile Met Asp Ile Gln Val Pro Thr Arg Ala Pro Asp  
 35 40 45

Ala Val Tyr Thr Glu Leu Gln Pro Thr Ser Pro Thr Pro Thr Trp Pro  
 50 55 60

Ala Asp Glu Thr Pro Gln Pro Gln Thr Gln Thr Gln Gln Leu Glu Gly  
 65 70 75 80

Thr Asp Gly Pro Leu Val Thr Asp Pro Glu Thr His Lys Ser Thr Lys  
 85 90 95

Ala Ala His Pro Thr Asp Asp Thr Thr Thr Leu Ser Glu Arg Pro Ser  
 100 105 110

Pro Ser Thr Asp Val Gln Thr Asp Pro Gln Thr Leu Lys Pro Ser Gly  
 115 120 125

Phe His Glu Asp Asp Pro Phe Phe Tyr Asp Glu His Thr Leu Arg Lys  
 130 135 140

Arg Gly Leu Leu Val Ala Ala Val Leu Phe Ile Thr Gly Ile Ile Ile  
 145 150 155 160

Leu Thr Ser Gly Lys Cys Arg Gln Leu Ser Arg Leu Cys Arg Asn His  
 165 170 175

Cys Arg

&lt;210&gt; 174

&lt;211&gt; 237

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 174

Met Leu Gly Gly Ser Leu Gly Ser Arg Leu Leu Arg Gly Val Gly Gly  
1 5 10 15

Ser His Gly Arg Phe Gly Ala Arg Gly Val Arg Glu Gly Gly Ala Ala  
20 25 30

Met Ala Ala Gly Glu Ser Met Ala Gln Arg Met Val Trp Val Asp Leu  
35 40 45

Glu Met Thr Gly Leu Asp Ile Glu Lys Asp Gln Ile Ile Glu Met Ala  
50 55 60

Cys Leu Ile Thr Asp Ser Asp Leu Asn Ile Leu Ala Glu Gly Pro Asn  
65 70 75 80

Leu Ile Ile Lys Gln Pro Asp Glu Leu Leu Asp Ser Met Ser Asp Trp  
85 90 95

Cys Lys Glu His His Gly Arg Ser Gly Leu Thr Lys Ala Val Lys Glu  
100 105 110

Ser Thr Ile Thr Leu Gln Gln Ala Glu Tyr Glu Phe Leu Ser Phe Val  
115 120 125

Arg Gln Gln Thr Pro Pro Gly Leu Cys Pro Leu Ala Gly Asn Ser Val  
130 135 140

His Glu Asp Lys Lys Phe Leu Asp Lys Tyr Met Pro Gln Phe Met Lys  
145 150 155 160

His Leu His Tyr Arg Ile Ile Asp Val Ser Thr Val Lys Glu Leu Cys  
165 170 175

Arg Arg Trp Tyr Pro Glu Glu Tyr Glu Phe Ala Pro Lys Lys Ala Ala  
180 185 190

Ser His Arg Ala Leu Asp Asp Ile Ser Glu Ser Ile Lys Glu Leu Gln  
195 200 205

Phe Tyr Arg Asn Asn Ile Phe Lys Lys Lys Ile Asp Glu Lys Lys Arg  
210 215 220

Lys Ile Ile Glu Asn Gly Glu Asn Glu Lys Thr Val Ser



225

230

235

<210> 175  
 <211> 390  
 <212> PRT  
 <213> Homo sapiens

<400> 175

Met Gly Gln Arg Leu Ser Gly Gly Arg Ser Cys Leu Asp Val Pro Gly  
 1 5 10 15

Arg Leu Leu Pro Gln Pro Pro Pro Pro Pro Pro Pro Val Arg Arg Lys  
 20 25 30

Leu Ala Leu Leu Phe Ala Met Leu Cys Val Trp Leu Tyr Met Phe Leu  
 35 40 45

Tyr Ser Cys Ala Gly Ser Cys Ala Ala Ala Pro Gly Leu Leu Leu Leu  
 50 55 60

Gly Ser Gly Ser Arg Ala Ala His Asp Pro Pro Ala Leu Ala Thr Ala  
 65 70 75 80

Pro Asp Gly Thr Pro Pro Arg Leu Pro Phe Arg Ala Pro Pro Ala Thr  
 85 90 95

Pro Leu Ala Ser Gly Lys Glu Met Ala Glu Gly Ala Ala Ser Pro Glu  
 100 105 110

Glu Gln Ser Pro Glu Val Pro Asp Ser Pro Ser Pro Ile Ser Ser Phe  
 115 120 125

Phe Ser Gly Ser Gly Ser Lys Gln Leu Pro Gln Ala Ile Ile Ile Gly  
 130 135 140

Val Lys Lys Gly Gly Thr Arg Ala Leu Leu Glu Phe Leu Arg Val His  
 145 150 155 160

Pro Asp Val Arg Ala Val Gly Ala Glu Pro His Phe Phe Asp Arg Ser  
 165 170 175

Tyr Asp Lys Gly Leu Ala Trp Tyr Arg Asp Leu Met Pro Arg Thr Leu  
 180 185 190

Asp Gly Gln Ile Thr Met Glu Lys Thr Pro Ser Tyr Phe Val Thr Arg  
 195 200 205

Glu Ala Pro Ala Arg Ile Ser Ala Met Ser Lys Asp Thr Lys Leu Ile  
 210 215 220

Val Val Val Arg Asp Pro Val Thr Arg Ala Ile Ser Asp Tyr Thr Gln  
 225 230 235 240

Thr Leu Ser Lys Arg Pro Asp Ile Pro Thr Phe Glu Ser Leu Thr Phe  
 245 250 255

Lys Asn Arg Thr Ala Gly Leu Ile Asp Thr Ser Trp Ser Ala Ile Gln  
 260 265 270

Ile Gly Ile Tyr Ala Lys His Leu Glu His Trp Leu Arg His Phe Pro  
 275 280 285

Ile Arg Gln Met Leu Phe Val Ser Gly Glu Arg Leu Ile Ser Asp Pro  
 290 295 300

Ala Gly Glu Leu Gly Arg Val Gln Asp Phe Leu Gly Leu Lys Arg Ile  
 305 310 315 320

Ile Thr Asp Lys His Phe Tyr Phe Asn Lys Thr Lys Gly Phe Pro Cys  
 325 330 335

Leu Lys Lys Ala Glu Gly Ser Ser Arg Pro His Cys Leu Gly Lys Thr  
 340 345 350

Lys Gly Arg Thr His Pro Glu Ile Asp Arg Glu Val Val Arg Arg Leu  
 355 360 365

Arg Glu Phe Tyr Arg Pro Phe Asn Leu Lys Phe Tyr Gln Met Thr Gly  
 370 375 380

His Asp Phe Gly Trp Asp  
 385 390

<210> 176  
 <211> 742  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 176

Met Asp Lys Phe Trp Trp His Ala Ala Trp Gly Leu Cys Leu Val Pro  
 1 5 10 15

Leu Ser Leu Ala Gln Ile Asp Leu Asn Ile Thr Cys Arg Phe Ala Gly  
 20 25 30

Val Phe His Val Glu Lys Asn Gly Arg Tyr Ser Ile Ser Arg Thr Glu  
 35 40 45

Ala Ala Asp Leu Cys Lys Ala Phe Asn Ser Thr Leu Pro Thr Met Ala  
 50 55 60

Gln Met Glu Lys Ala Leu Ser Ile Gly Phe Glu Thr Cys Arg Tyr Gly  
 65 70 75 80

Phe Ile Glu Gly His Val Val Ile Pro Arg Ile His Pro Asn Ser Ile  
 85 90 95

Cys Ala Ala Asn Asn Thr Gly Val Tyr Ile Leu Thr Tyr Asn Thr Ser  
 100 105 110

Gln Tyr Asp Thr Tyr Cys Phe Asn Ala Ser Ala Pro Pro Glu Glu Asp  
 115 120 125

Cys Thr Ser Val Thr Asp Leu Pro Asn Ala Phe Asp Gly Pro Ile Thr  
 130 135 140

Ile Thr Ile Val Asn Arg Asp Gly Thr Arg Tyr Val Gln Lys Gly Glu  
 145 150 155 160

Tyr Arg Thr Asn Pro Glu Asp Ile Tyr Pro Ser Asn Pro Thr Asp Asp  
 165 170 175

Asp Val Ser Ser Gly Ser Ser Ser Glu Arg Ser Ser Thr Ser Gly Gly  
 180 185 190

Tyr Ile Phe Tyr Thr Phe Ser Thr Val His Pro Ile Pro Asp Glu Asp  
 195 200 205

Ser Pro Trp Ile Thr Asp Ser Thr Asp Arg Ile Pro Ala Thr Thr Leu  
 210 215 220

Met Ser Thr Ser Ala Thr Ala Thr Glu Thr Ala Thr Lys Arg Gln Glu  
225 230 235 240

Ala Trp Asp Trp Phe Ser Trp Leu Phe Leu Pro Ser Glu Ser Lys Asn  
245 250 255

His Leu His Thr Thr Thr Gln Met Ala Gly Thr Ser Ser Asn Thr Ile  
260 265 270

Ser Ala Gly Trp Glu Pro Asn Glu Glu Asn Glu Asp Glu Arg Asp Arg  
275 280 285

His Leu Ser Phe Ser Gly Ser Gly Ile Asp Asp Asp Glu Asp Phe Ile  
290 295 300

Ser Ser Thr Ile Ser Thr Thr Pro Arg Ala Phe Asp His Thr Lys Gln  
305 310 315 320

Asn Gln Asp Trp Thr Gln Trp Asn Pro Ser His Ser Asn Pro Glu Val  
325 330 335

Leu Leu Gln Thr Thr Thr Arg Met Thr Asp Val Asp Arg Asn Gly Thr  
340 345 350

Thr Ala Tyr Glu Gly Asn Trp Asn Pro Glu Ala His Pro Pro Leu Ile  
355 360 365

His His Glu His His Glu Glu Glu Glu Thr Pro His Ser Thr Ser Thr  
370 375 380

Ile Gln Ala Thr Pro Ser Ser Thr Thr Glu Glu Thr Ala Thr Gln Lys  
385 390 395 400

Glu Gln Trp Phe Gly Asn Arg Trp His Glu Gly Tyr Arg Gln Thr Pro  
405 410 415

Arg Glu Asp Ser His Ser Thr Thr Gly Thr Ala Ala Ala Ser Ala His  
420 425 430

Thr Ser His Pro Met Gln Gly Arg Thr Thr Pro Ser Pro Glu Asp Ser  
435 440 445

Ser Trp Thr Asp Phe Phe Asn Pro Ile Ser His Pro Met Gly Arg Gly  
 450 455 460

His Gln Ala Gly Arg Arg Met Asp Met Asp Ser Ser His Ser Thr Thr  
 465 470 475 480

Leu Gln Pro Thr Ala Asn Pro Asn Thr Gly Leu Val Glu Asn Leu Asp  
 485 490 495

Arg Thr Gly Pro Leu Ser Met Thr Thr Gln Gln Ser Asn Ser Gln Ser  
 500 505 510

Phe Ser Thr Ser His Glu Gly Leu Glu Glu Asp Lys Asp His Pro Thr  
 515 520 525

Thr Ser Thr Leu Thr Ser Ser Asn Arg Asn Asp Val Thr Gly Gly Arg  
 530 535 540

Arg Asp Pro Asn His Ser Glu Gly Ser Thr Thr Leu Leu Glu Gly Tyr  
 545 550 555 560

Thr Ser His Tyr Pro His Thr Lys Glu Ser Arg Thr Phe Ile Pro Val  
 565 570 575

Thr Ser Ala Lys Thr Gly Ser Phe Gly Val Thr Ala Val Thr Val Gly  
 580 585 590

Asp Ser Asn Ser Asn Val Asn Arg Ser Leu Ser Gly Asp Gln Asp Thr  
 595 600 605

Phe His Pro Ser Gly Gly Ser His Thr Thr His Gly Ser Glu Ser Asp  
 610 615 620

Gly His Ser His Gly Ser Gln Glu Gly Gly Ala Asn Thr Thr Ser Gly  
 625 630 635 640

Pro Ile Arg Thr Pro Gln Ile Pro Glu Trp Leu Ile Ile Leu Ala Ser  
 645 650 655

Leu Leu Ala Leu Ala Leu Ile Leu Ala Val Cys Ile Ala Val Asn Ser  
 660 665 670

Arg Arg Arg Cys Gly Gln Lys Lys Lys Leu Val Ile Asn Ser Gly Asn  
 675 680 685

Gly Ala Val Glu Asp Arg Lys Pro Ser Gly Leu Asn Gly Glu Ala Ser  
 690 695 700

Lys Ser Gln Glu Met Val His Leu Val Asn Lys Glu Ser Ser Glu Thr  
 705 710 715 720

Pro Asp Gln Phe Met Thr Ala Asp Glu Thr Arg Asn Leu Gln Asn Val  
 725 730 735

Asp Met Lys Ile Gly Val  
 740

<210> 177  
 <211> 251  
 <212> PRT  
 <213> Homo sapiens  
 <400> 177

Met Ala Gly Thr Thr Asp Arg Glu Glu Ala Thr Arg Leu Leu Ala Glu  
 1 5 10 15

Lys Arg Arg Gln Ala Arg Glu Gln Arg Glu Arg Glu Glu Gln Glu Arg  
 20 25 30

Arg Leu Gln Ala Glu Arg Asp Lys Arg Met Arg Glu Glu Gln Leu Ala  
 35 40 45

Arg Glu Ala Glu Ala Arg Ala Glu Arg Glu Ala Glu Ala Arg Arg Arg  
 50 55 60

Glu Glu Gln Glu Ala Arg Glu Lys Ala Gln Ala Glu Gln Glu Glu Gln  
 65 70 75 80

Glu Arg Leu Gln Lys Gln Lys Glu Glu Ala Glu Ala Arg Ser Arg Glu  
 85 90 95

Glu Ala Glu Arg Gln Arg Leu Glu Arg Glu Lys His Phe Gln Gln Gln  
 100 105 110

Glu Gln Glu Arg Gln Glu Arg Arg Lys Arg Leu Glu Glu Ile Met Lys  
 115 120 125

Arg Thr Arg Lys Ser Glu Val Ser Glu Thr Lys Lys Gln Asp Ser Lys  
 130 135 140

Glu Ala Asn Ala Asn Gly Ser Ser Pro Glu Pro Val Lys Ala Val Glu  
 145 150 155 160

Ala Arg Ser Pro Gly Leu Gln Lys Glu Ala Val Gln Lys Glu Glu Pro  
 165 170 175

Ile Pro Gln Glu Pro Gln Trp Ser Leu Pro Ser Lys Glu Leu Pro Ala  
 180 185 190

Ser Leu Val Asn Gly Leu Gln Pro Leu Pro Ala His Gln Glu Asn Gly  
 195 200 205

Phe Ser Thr Asn Gly Pro Ser Gly Asp Lys Ser Leu Ser Arg Thr Pro  
 210 215 220

Glu Thr Leu Leu Pro Phe Ala Glu Ala Glu Ala Phe Leu Lys Lys Ala  
 225 230 235 240

Val Val Gln Ser Pro Gln Val Thr Glu Val Leu  
 245 250

<210> 178  
 <211> 71  
 <212> PRT  
 <213> Homo sapiens

<400> 178

Ser Ser Lys Thr Ala Ser Thr Asn Asn Ile Ala Gln Ala Arg Arg Thr  
 1 5 10 15

Val Gln Gln Leu Arg Leu Glu Ala Ser Ile Glu Arg Ile Lys Val Ser  
 20 25 30

Lys Ala Ser Ala Asp Leu Met Ser Tyr Cys Glu Glu His Ala Arg Ser  
 35 40 45

Asp Pro Leu Leu Ile Gly Ile Pro Thr Ser Glu Asn Pro Phe Lys Asp  
 50 55 60

Lys Lys Thr Cys Ile Ile Leu  
65 70

<210> 179  
<211> 292  
<212> PRT  
<213> Homo sapiens

<400> 179

Met Asn Leu Asn Met Gly Arg Glu Met Lys Glu Glu Leu Glu Glu Glu  
1 5 10 15

Glu Lys Met Arg Glu Asp Gly Gly Gly Lys Asp Arg Ala Lys Ser Lys  
20 25 30

Lys Val His Arg Ile Val Ser Lys Trp Met Leu Pro Glu Lys Ser Arg  
35 40 45

Gly Thr Tyr Leu Glu Arg Ala Asn Cys Phe Pro Pro Pro Val Phe Ile  
50 55 60

Ile Ser Ile Ser Leu Ala Glu Leu Ala Val Phe Ile Tyr Tyr Ala Val  
65 70 75 80

Trp Lys Pro Gln Lys Gln Trp Ile Thr Leu Asp Thr Gly Ile Leu Glu  
85 90 95

Ser Pro Phe Ile Tyr Ser Pro Glu Lys Arg Glu Glu Ala Trp Arg Phe  
100 105 110

Ile Ser Tyr Met Leu Val His Ala Gly Val Gln His Ile Leu Gly Asn  
115 120 125

Leu Cys Met Gln Leu Val Leu Gly Ile Pro Leu Glu Met Val His Lys  
130 135 140

Gly Leu Arg Val Gly Leu Val Tyr Leu Ala Gly Val Ile Ala Gly Ser  
145 150 155 160

Leu Ala Ser Ser Ile Phe Asp Pro Leu Arg Tyr Leu Val Gly Ala Ser  
165 170 175

Gly Gly Val Tyr Ala Leu Met Gly Gly Tyr Phe Met Asn Val Leu Val  
180 185 190



Asn Phe Gln Glu Met Ile Pro Ala Phe Gly Ile Phe Arg Leu Leu Ile  
 195 200 205

Ile Ile Leu Ile Ile Val Leu Asp Met Gly Phe Ala Leu Tyr Arg Arg  
 210 215 220

Phe Phe Val Pro Glu Asp Gly Ser Pro Val Ser Phe Ala Ala His Ile  
 225 230 235 240

Ala Gly Gly Phe Ala Gly Met Ser Ile Gly Tyr Thr Val Phe Ser Cys  
 245 250 255

Phe Asp Lys Ala Leu Leu Lys Asp Pro Arg Phe Trp Ile Ala Ile Ala  
 260 265 270

Ala Tyr Leu Ala Cys Val Leu Phe Ala Val Phe Phe Asn Ile Phe Leu  
 275 280 285

Ser Pro Ala Asn  
 290

<210> 180  
 <211> 775  
 <212> PRT  
 <213> Homo sapiens

<400> 180

Met Ala Ser Arg Ala Val Val Arg Ala Arg Arg Cys Pro Gln Cys Pro  
 1 5 10 15

Gln Val Arg Ala Ala Ala Ala Ala Pro Ala Trp Ala Ala Leu Pro Leu  
 20 25 30

Ser Arg Ser Leu Pro Pro Cys Ser Asn Ser Ser Ser Phe Ser Met Pro  
 35 40 45

Leu Phe Leu Leu Leu Leu Leu Val Leu Leu Leu Leu Leu Glu Asp Ala  
 50 55 60

Gly Ala Gln Gln Gly Asp Gly Cys Gly His Thr Val Leu Gly Pro Glu  
 65 70 75 80

Ser Gly Thr Leu Thr Ser Ile Asn Tyr Pro Gln Thr Tyr Pro Asn Ser  
85 90 95

Thr Val Cys Glu Trp Glu Ile Arg Val Lys Met Gly Glu Arg Val Arg  
100 105 110

Ile Lys Phe Gly Asp Phe Asp Ile Glu Asp Ser Asp Ser Cys His Phe  
115 120 125

Asn Tyr Leu Arg Ile Tyr Asn Gly Ile Gly Val Ser Arg Thr Glu Ile  
130 135 140

Gly Lys Tyr Cys Gly Leu Gly Leu Gln Met Asn His Ser Ile Glu Ser  
145 150 155 160

Lys Gly Asn Glu Ile Thr Leu Leu Phe Met Ser Gly Ile His Val Ser  
165 170 175

Gly Arg Gly Phe Leu Ala Ser Tyr Ser Val Ile Asp Lys Gln Asp Leu  
180 185 190

Ile Thr Cys Leu Asp Thr Ala Ser Asn Phe Leu Glu Pro Glu Phe Ser  
195 200 205

Lys Tyr Cys Pro Ala Gly Cys Leu Leu Pro Phe Ala Glu Ile Ser Gly  
210 215 220

Thr Ile Pro His Gly Tyr Arg Asp Ser Ser Pro Leu Cys Met Ala Gly  
225 230 235 240

Val His Ala Gly Val Val Ser Asn Thr Leu Gly Gly Gln Ile Ser Val  
245 250 255

Val Ile Ser Lys Gly Ile Pro Tyr Tyr Glu Ser Ser Leu Ala Asn Asn  
260 265 270

Val Thr Ser Val Val Gly His Leu Ser Thr Ser Leu Phe Thr Phe Lys  
275 280 285

Thr Ser Gly Cys Tyr Gly Thr Leu Gly Met Glu Ser Gly Val Ile Ala  
290 295 300

Asp Pro Gln Ile Thr Ala Ser Ser Val Leu Glu Trp Thr Asp His Thr

305	310	315	320
Gly Gln Glu Asn Ser Trp Lys Pro Lys Lys Ala Arg Leu Lys Lys Pro	325	330	335
Gly Pro Pro Trp Ala Ala Phe Ala Thr Asp Glu Tyr Gln Trp Leu Gln	340	345	350
Ile Asp Leu Asn Lys Glu Lys Lys Ile Thr Gly Ile Ile Thr Thr Gly	355	360	365
Ser Thr Met Val Glu His Asn Tyr Tyr Val Ser Ala Tyr Arg Ile Leu	370	375	380
Tyr Ser Asp Asp Gly Gln Lys Trp Thr Val Tyr Arg Glu Pro Gly Val	385	390	395
Glu Gln Asp Lys Ile Phe Gln Gly Asn Lys Asp Tyr His Gln Asp Val	405	410	415
Arg Asn Asn Phe Leu Pro Pro Ile Ile Ala Arg Phe Ile Arg Val Asn	420	425	430
Pro Thr Gln Trp Gln Gln Lys Ile Ala Met Lys Met Glu Leu Leu Gly	435	440	445
Cys Gln Phe Ile Pro Lys Gly Arg Pro Pro Lys Leu Thr Gln Pro Pro	450	455	460
Pro Pro Arg Asn Ser Asn Asp Leu Lys Asn Thr Thr Ala Pro Pro Lys	465	470	475
Ile Ala Lys Gly Arg Ala Pro Lys Phe Thr Gln Pro Leu Gln Pro Arg	485	490	495
Ser Ser Asn Glu Phe Pro Ala Gln Thr Glu Gln Thr Thr Ala Ser Pro	500	505	510
Asp Ile Arg Asn Thr Thr Val Thr Pro Asn Val Thr Lys Asp Val Ala	515	520	525
Leu Ala Ala Val Leu Val Pro Val Leu Val Met Val Leu Thr Thr Leu	530	535	540

Ile Leu Ile Leu Val Cys Ala Trp His Trp Arg Asn Arg Lys Lys Lys  
 545 550 555 560

Thr Glu Gly Thr Tyr Asp Leu Pro Tyr Trp Asp Arg Ala Gly Trp Trp  
 565 570 575

Lys Gly Met Lys Gln Phe Leu Pro Ala Lys Ala Val Asp His Glu Glu  
 580 585 590

Thr Pro Val Arg Tyr Ser Ser Ser Glu Val Asn His Leu Ser Pro Arg  
 595 600 605

Glu Val Thr Thr Val Leu Gln Ala Asp Ser Ala Glu Tyr Ala Gln Pro  
 610 615 620

Leu Val Gly Gly Ile Val Gly Thr Leu His Gln Arg Ser Thr Phe Lys  
 625 630 635 640

Pro Glu Glu Gly Lys Glu Ala Gly Tyr Ala Asp Leu Asp Pro Tyr Asn  
 645 650 655

Ser Pro Gly Gln Glu Val Tyr His Ala Tyr Ala Glu Pro Leu Pro Ile  
 660 665 670

Thr Gly Pro Glu Tyr Ala Thr Pro Ile Ile Met Asp Met Ser Gly His  
 675 680 685

Pro Thr Thr Ser Val Gly Gln Pro Ser Thr Ser Thr Phe Lys Ala Thr  
 690 695 700

Gly Asn Gln Pro Pro Pro Leu Val Gly Thr Tyr Asn Thr Leu Leu Ser  
 705 710 715 720

Arg Thr Asp Ser Cys Ser Ser Ala Gln Ala Gln Tyr Asp Thr Pro Lys  
 725 730 735

Ala Gly Lys Pro Gly Leu Pro Ala Pro Asp Glu Leu Val Tyr Gln Val  
 740 745 750

Pro Gln Ser Thr Gln Glu Val Ser Gly Ala Gly Arg Asp Gly Glu Cys  
 755 760 765

Asp Val Phe Lys Glu Ile Leu  
770 775

<210> 181  
<211> 494  
<212> PRT  
<213> Homo sapiens

<400> 181

Glu Asn Tyr Lys Asn Leu Val Ala Val Asp Trp Glu Ser His Ile Asn  
1 5 10 15

Thr Lys Trp Ser Ala Pro Gln Gln Asn Phe Leu Gln Gly Lys Thr Ser  
20 25 30

Ser Val Val Glu Met Glu Arg Asn His Phe Gly Glu Glu Leu Phe Asp  
35 40 45

Phe Asn Gln Cys Glu Lys Ala Leu Ser Glu His Ser Cys Leu Lys Thr  
50 55 60

His Arg Arg Thr Tyr Phe Arg Lys Lys Thr Cys Glu Cys Asn Gln Cys  
65 70 75 80

Glu Lys Ala Phe Arg Lys Pro Ser Ile Phe Thr Leu His Lys Lys Thr  
85 90 95

Asp Ile Gly Glu Glu Leu Pro Asn Cys Asn Gln Cys Glu Thr Ala Phe  
100 105 110

Ser Gln His Leu His Leu Val Cys Lys Lys Thr Ser Gln Asn Leu His  
115 120 125

Leu Val Cys Lys Lys Thr His Thr Gln Glu Lys Pro Tyr Lys Cys Ser  
130 135 140

Asp Cys Glu Lys Gly Leu Pro Ser Ser Ser His Leu Arg Glu Cys Val  
145 150 155 160

Arg Ile Tyr Gly Gly Glu Arg Pro Tyr Thr His Lys Glu Tyr Val Glu  
165 170 175

Thr Phe Ser His Ser Thr Ala Leu Phe Val His Met Gln Thr Gln Asp

180	185	190
Gly Glu Lys Phe Tyr Glu Cys Lys Ala Cys Gly Lys Pro Phe Thr Glu		
195	200	205
Ser Ser Tyr Leu Thr Gln His Leu Arg Thr His Ser Arg Val Leu Pro		
210	215	220
Ile Glu His Lys Lys Phe Gly Lys Ala Phe Ala Phe Ser Pro Asp Leu		
225	230	235
Ala Lys His Ile Arg Leu Arg Thr Arg Gly Lys His Tyr Val Cys Asn		
245	250	255
Glu Cys Gly Lys Glu Phe Thr Cys Phe Ser Lys Leu Asn Ile His Ile		
260	265	270
Arg Val His Thr Gly Glu Lys Pro Tyr Glu Cys Asn Lys Cys Gly Lys		
275	280	285
Ala Phe Thr Asp Ser Ser Gly Leu Ile Lys His Arg Arg Thr His Thr		
290	295	300
Gly Glu Lys Pro Tyr Glu Cys Lys Glu Cys Gly Lys Ala Phe Ala Asn		
305	310	315
Ser Ser His Leu Thr Val His Met Arg Thr His Thr Gly Glu Lys Pro		
325	330	335
Tyr Gln Cys Lys Glu Cys Gly Lys Ala Phe Ile Asn Ser Ser Ser Phe		
340	345	350
Lys Ser His Met Gln Thr His Pro Gly Val Lys Pro Tyr Asp Cys Gln		
355	360	365
Gln Cys Gly Lys Ala Phe Ile Arg Ser Ser Phe Leu Ile Arg His Leu		
370	375	380
Arg Ser His Ser Ala Glu Arg Pro Phe Glu Cys Glu Glu Cys Gly Lys		
385	390	395
Ala Phe Arg Tyr Ser Ser His Leu Ser Gln His Lys Arg Ile His Thr		
405	410	415

Gly Glu Arg Pro Tyr Lys Cys Gln Lys Cys Gly Gln Ala Phe Ser Ile  
 420 425 430

Ser Ser Gly Leu Thr Val His Met Arg Thr His Thr Gly Glu Arg Pro  
 435 440 445

Phe Glu Cys Gln Glu Cys Gly Lys Ala Phe Thr Arg Ser Thr Tyr Leu  
 450 455 460

Ile Arg His Leu Arg Ser His Ser Val Glu Lys Pro Tyr Lys Glu Cys  
 465 470 475 480

Gly Gln Thr Phe Ser Asn Ser Ser Cys Leu Thr Glu Cys Val  
 485 490

<210> 182  
 <211> 556  
 <212> PRT  
 <213> Homo sapiens

<400> 182

Met Met Asn Lys Leu Tyr Ile Gly Asn Leu Ser Pro Ala Val Thr Ala  
 1 5 10 15

Asp Asp Leu Arg Gln Leu Phe Gly Asp Arg Lys Leu Pro Leu Ala Gly  
 20 25 30

Gln Val Leu Leu Lys Ser Gly Tyr Ala Phe Val Asp Tyr Pro Asp Gln  
 35 40 45

Asn Trp Ala Ile Arg Ala Ile Glu Thr Leu Ser Gly Lys Val Glu Leu  
 50 55 60

His Gly Lys Ile Met Glu Val Asp Tyr Ser Val Ser Lys Lys Leu Arg  
 65 70 75 80

Ser Arg Lys Ile Gln Ile Arg Asn Ile Pro Pro His Leu Gln Trp Glu  
 85 90 95

Val Leu Asp Gly Leu Leu Ala Gln Tyr Gly Thr Val Glu Asn Val Glu  
 100 105 110

Gln Val Asn Thr Asp Thr Glu Thr Ala Val Val Asn Val Thr Tyr Ala  
 115 120 125

Thr Arg Glu Glu Ala Lys Ile Ala Met Glu Lys Leu Ser Gly His Gln  
 130 135 140

Phe Glu Asn Tyr Ser Phe Lys Ile Ser Tyr Ile Pro Asp Glu Glu Val  
 145 150 155 160

Ser Ser Pro Ser Pro Pro Gln Arg Ala Gln Arg Gly Asp His Ser Ser  
 165 170 175

Arg Glu Gln Gly His Ala Pro Gly Gly Thr Ser Gln Ala Arg Gln Ile  
 180 185 190

Asp Phe Pro Leu Arg Ile Leu Val Pro Thr Gln Phe Val Gly Ala Ile  
 195 200 205

Ile Gly Lys Glu Gly Leu Thr Ile Lys Asn Ile Thr Lys Gln Thr Gln  
 210 215 220

Ser Arg Val Asp Ile His Arg Lys Glu Asn Ser Gly Ala Ala Glu Lys  
 225 230 235 240

Pro Val Thr Ile His Ala Thr Pro Glu Gly Thr Ser Glu Ala Cys Arg  
 245 250 255

Met Ile Leu Glu Ile Met Gln Lys Glu Ala Asp Glu Thr Lys Leu Ala  
 260 265 270

Glu Glu Ile Pro Leu Lys Ile Leu Ala His Asn Gly Leu Val Gly Arg  
 275 280 285

Leu Ile Gly Lys Glu Gly Arg Asn Leu Lys Lys Ile Glu His Glu Thr  
 290 295 300

Gly Thr Lys Ile Thr Ile Ser Ser Leu Gln Asp Leu Ser Ile Tyr Asn  
 305 310 315 320

Pro Glu Arg Thr Ile Thr Val Lys Gly Thr Val Glu Ala Cys Ala Ser  
 325 330 335

Ala Glu Ile Glu Ile Met Lys Lys Leu Arg Glu Ala Phe Glu Asn Asp



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&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 183

Met Ser Asp Ile Leu Arg Glu Leu Leu Cys Val Ser Glu Lys Ala Ala  
 1 5 10 15

Asn Ile Ala Arg Ala Cys Arg Gln Gln Glu Ala Leu Phe Gln Leu Leu  
 20 25 30

Ile Glu Glu Lys Lys Glu Gly Glu Lys Asn Lys Lys Phe Ala Val Asp  
 35 40 45

Phe Lys Thr Leu Ala Asp Val Leu Val Gln Glu Val Ile Lys Gln Asn  
 50 55 60

Met Glu Asn Lys Phe Pro Gly Leu Glu Lys Asn Ile Phe Gly Glu Glu  
 65 70 75 80

Ser Asn Glu Phe Thr Asn Asp Trp Gly Glu Lys Ile Thr Leu Arg Leu  
 85 90 95

Cys Ser Thr Glu Glu Glu Thr Ala Glu Leu Leu Ser Lys Val Leu Asn  
 100 105 110

Gly Asn Lys Val Ala Ser Glu Ala Leu Ala Arg Val Val His Gln Asp  
 115 120 125

Val Ala Phe Thr Asp Pro Thr Leu Asp Ser Thr Glu Ile Asn Val Pro  
 130 135 140

Gln Asp Ile Leu Gly Ile Trp Val Asp Pro Ile Asp Ser Thr Tyr Gln  
 145 150 155 160

Tyr Ile Lys Gly Ser Ala Asp Ile Lys Ser Asn Gln Gly Ile Phe Pro  
 165 170 175

Cys Gly Leu Gln Cys Val Thr Ile Leu Ile Gly Val Tyr Asp Ile Gln  
 180 185 190

Thr Gly Val Pro Leu Met Gly Val Ile Asn Gln Pro Phe Val Ser Arg  
 195 200 205

Asp Pro Asn Thr Leu Arg Trp Lys Gly Gln Cys Tyr Trp Gly Leu Ser  
 210 215 220

Tyr Met Gly Thr Asn Met His Ser Leu Gln Leu Thr Ile Ser Arg Arg  
 225 230 235 240

Asn Gly Ser Glu Thr His Thr Gly Asn Thr Gly Ser Glu Ala Ala Phe  
 245 250 255

Ser Pro Ser Phe Ser Ala Val Ile Ser Thr Ser Glu Lys Glu Thr Ile  
 260 265 270

Lys Ala Ala Leu Ser Arg Val Cys Gly Asp Arg Ile Phe Gly Ala Ala  
 275 280 285

Gly Ala Gly Tyr Lys Ser Leu Cys Val Val Gln Gly Leu Val Asp Ile  
 290 295 300

Tyr Ile Phe Ser Glu Asp Thr Thr Phe Lys Trp Asp Ser Cys Ala Ala  
 305 310 315 320

His Ala Ile Leu Arg Ala Met Gly Gly Gly Ile Val Asp Leu Lys Glu  
 325 330 335

Cys Leu Glu Arg Asn Pro Glu Thr Gly Leu Asp Leu Pro Gln Leu Val  
 340 345 350

Tyr His Val Glu Asn Glu Gly Ala Ala Gly Val Asp Arg Trp Ala Asn  
 355 360 365

Lys Gly Gly Leu Ile Ala Tyr Arg Ser Arg Lys Arg Leu Glu Thr Phe  
 370 375 380

Leu Ser Leu Leu Val Gln Asn Leu Ala Pro Ala Glu Thr His Thr  
 385 390 395

<210> 184  
 <211> 662  
 <212> PRT  
 <213> Homo sapiens

<400> 184

Pro Leu Cys Pro Ala Leu Cys Pro Thr Ser Pro Pro Pro Leu Pro Leu  
 1 5 10 15

Leu Pro Pro Ser Val Ser Pro Pro Gly Cys Leu Thr Leu Trp Ser Leu  
 20 25 30

Ser Phe Leu Phe Ser Val Pro Ser Ala Pro Tyr Pro His Leu Lys Thr  
 35 40 45

Thr Met Ala Thr Ile Pro Asp Trp Lys Leu Gln Leu Leu Ala Arg Arg  
 50 55 60

Arg Gln Glu Glu Ala Ser Val Arg Gly Arg Glu Lys Ala Glu Arg Glu  
 65 70 75 80

Arg Leu Ser Gln Met Pro Ala Trp Lys Arg Gly Leu Leu Glu Arg Arg  
 85 90 95

Arg Ala Lys Leu Gly Leu Ser Pro Gly Glu Pro Ser Pro Val Leu Gly  
 100 105 110

Thr Val Glu Ala Gly Pro Pro Asp Pro Asp Glu Ser Ala Val Leu Leu  
 115 120 125

Glu Ala Ile Gly Pro Val His Gln Asn Arg Phe Ile Arg Gln Glu Arg  
 130 135 140

Gln Gln Gln Gln Gln Gln Gln Arg Ser Glu Glu Leu Leu Ala Glu  
 145 150 155 160

Arg Lys Pro Gly Pro Leu Glu Ala Arg Glu Arg Arg Pro Ser Pro Gly  
 165 170 175

Glu Met Arg Asp Gln Ser Pro Lys Gly Arg Glu Ser Arg Glu Glu Arg  
 180 185 190

Leu Ser Pro Arg Glu Thr Arg Glu Arg Arg Leu Gly Ile Gly Gly Ala  
 195 200 205

Gln Glu Leu Ser Leu Arg Pro Leu Glu Ala Arg Asp Trp Arg Gln Ser  
 210 215 220

Pro Gly Glu Val Gly Asp Arg Ser Ser Arg Leu Ser Glu Ala Trp Lys  
 225 230 235 240

Trp Arg Leu Ser Pro Gly Glu Thr Pro Glu Arg Ser Leu Arg Leu Ala  
 245 250 255

Glu Ser Arg Glu Gln Ser Pro Arg Arg Lys Glu Val Glu Ser Arg Leu  
 260 265 270

Ser Pro Gly Glu Ser Ala Tyr Gln Lys Leu Gly Leu Thr Glu Ala His  
 275 280 285

Lys Trp Arg Pro Asp Ser Arg Glu Ser Gln Glu Gln Ser Leu Val Gln  
 290 295 300

Leu Glu Ala Thr Glu Trp Arg Leu Arg Ser Gly Glu Glu Arg Gln Asp  
 305 310 315 320

Tyr Ser Glu Glu Cys Gly Arg Lys Glu Glu Trp Pro Val Pro Gly Val  
 325 330 335

Ala Pro Lys Glu Thr Ala Glu Leu Ser Glu Thr Leu Thr Arg Glu Ala  
 340 345 350

Gln Gly Asn Ser Ser Ala Gly Val Glu Ala Ala Glu Gln Arg Pro Val  
 355 360 365

Glu Asp Gly Glu Arg Gly Met Lys Pro Thr Glu Gly Trp Lys Trp Thr  
 370 375 380

Leu Asn Ser Gly Lys Ala Arg Glu Trp Thr Pro Arg Asp Ile Glu Ala  
 385 390 395 400

Gln Thr Gln Lys Pro Glu Pro Pro Glu Ser Ala Glu Lys Leu Leu Glu  
 405 410 415

Ser Pro Gly Val Glu Ala Gly Glu Gly Glu Ala Glu Lys Glu Glu Ala  
 420 425 430

Gly Ala Gln Gly Arg Pro Leu Arg Ala Leu Gln Asn Cys Cys Ser Val  
 435 440 445

Pro Ser Pro Leu Pro Pro Glu Asp Ala Gly Thr Gly Gly Leu Arg Gln  
 450 455 460

Gln Glu Glu Glu Ala Val Glu Leu Gln Pro Pro Pro Pro Ala Pro Leu  
 465 470 475 480

Ser Pro Pro Pro Pro Ala Pro Thr Ala Pro Gln Pro Pro Gly Asp Pro  
 485 490 495

Leu Met Ser Arg Leu Phe Tyr Gly Val Lys Ala Gly Pro Gly Val Gly  
 500 505 510

Ala Pro Arg Arg Ser Gly His Thr Phe Thr Val Asn Pro Arg Arg Ser  
 515 520 525

Val Pro Pro Ala Thr Pro Ala Thr Pro Thr Ser Pro Ala Thr Val Asp  
 530 535 540

Ala Ala Val Pro Gly Ala Gly Lys Lys Arg Tyr Pro Thr Ala Glu Glu  
 545 550 555 560

Ile Leu Val Leu Gly Gly Tyr Leu Arg Leu Ser Arg Ser Cys Leu Ala  
 565 570 575

Lys Gly Ser Pro Glu Arg His His Lys Gln Leu Lys Ile Ser Phe Ser  
 580 585 590

Glu Thr Ala Leu Glu Thr Thr Tyr Gln Tyr Pro Ser Glu Ser Ser Val  
 595 600 605

Leu Glu Glu Leu Gly Pro Glu Pro Glu Val Pro Ser Ala Pro Asn Pro  
 610 615 620

Pro Ala Ala Gln Pro Asp Asp Glu Glu Asp Glu Glu Glu Leu Leu Leu  
 625 630 635 640

Leu Gln Pro Glu Leu Gln Gly Gly Leu Arg Thr Lys Ala Leu Ile Val  
 645 650 655

Asp Glu Ser Cys Arg Arg  
 660

<210> 185

<211> 1609

<212> PRT

<213> Homo sapiens

&lt;400&gt; 185

Met Arg Gly Ser His Arg Ala Ala Pro Ala Leu Arg Pro Arg Gly Arg  
 1 5 10 15

Leu Trp Pro Val Leu Ala Val Leu Ala Ala Ala Ala Ala Ala Gly Cys  
 20 25 30

Ala Gln Ala Ala Met Asp Glu Cys Thr Asp Glu Gly Gly Arg Pro Gln  
 35 40 45

Arg Cys Met Pro Glu Phe Val Asn Ala Ala Phe Asn Val Thr Val Val  
 50 55 60

Ala Thr Asn Thr Cys Gly Thr Pro Pro Glu Glu Tyr Cys Val Gln Thr  
 65 70 75 80

Gly Val Thr Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln  
 85 90 95

Pro His Leu Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln  
 100 105 110

Ala Asp Thr Thr Trp Trp Gln Ser Gln Thr Met Leu Ala Gly Val Gln  
 115 120 125

Tyr Pro Ser Ser Ile Asn Leu Thr Leu His Leu Gly Lys Ala Phe Asp  
 130 135 140

Ile Thr Tyr Val Arg Leu Lys Phe His Thr Ser Arg Pro Glu Ser Phe  
 145 150 155 160

Ala Ile Tyr Lys Arg Thr Arg Glu Asp Gly Pro Trp Ile Pro Tyr Gln  
 165 170 175

Tyr Tyr Ser Gly Ser Cys Glu Asn Thr Tyr Ser Lys Ala Asn Arg Gly  
 180 185 190

Phe Ile Arg Thr Gly Gly Asp Glu Gln Gln Ala Leu Cys Thr Asp Glu  
 195 200 205

Phe Ser Asp Phe Ser Pro Leu Thr Gly Gly Asn Val Ala Phe Ser Thr  
 210 215 220

Leu Glu Gly Arg Pro Ser Ala Tyr Asn Phe Asp Asn Ser Pro Val Leu  
 225 230 235 240

Gln Glu Trp Val Thr Ala Thr Asp Ile Arg Val Thr Leu Asn Arg Leu  
 245 250 255

Asn Thr Phe Gly Asp Glu Val Phe Asn Asp Pro Lys Val Leu Lys Ser  
 260 265 270

Tyr Tyr Tyr Ala Ile Ser Asp Phe Ala Val Gly Gly Arg Cys Lys Cys  
 275 280 285

Asn Gly His Ala Ser Glu Cys Met Lys Asn Glu Phe Asp Lys Leu Val  
 290 295 300

Cys Asn Cys Lys His Asn Thr Tyr Gly Val Asp Cys Glu Lys Cys Leu  
 305 310 315 320

Pro Phe Phe Asn Asp Arg Pro Trp Arg Arg Ala Thr Ala Glu Ser Ala  
 325 330 335

Ser Glu Cys Leu Pro Cys Asp Cys Asn Gly Arg Ser Gln Glu Cys Tyr  
 340 345 350

Phe Asp Pro Glu Leu Tyr Arg Ser Thr Gly His Gly Gly His Cys Thr  
 355 360 365

Asn Cys Gln Asp Asn Thr Asp Gly Ala His Cys Glu Arg Cys Arg Glu  
 370 375 380

Asn Phe Phe Arg Leu Gly Asn Asn Glu Ala Cys Ser Ser Cys His Cys  
 385 390 395 400

Ser Pro Val Gly Ser Leu Ser Thr Gln Cys Asp Ser Tyr Gly Arg Cys  
 405 410 415

Ser Cys Lys Pro Gly Val Met Gly Asp Lys Cys Asp Arg Cys Gln Pro  
 420 425 430

Gly Phe His Ser Leu Thr Glu Ala Gly Cys Arg Pro Cys Ser Cys Asp  
 435 440 445



Pro Ser Gly Ser Ile Asp Glu Cys Asn Val Glu Thr Gly Arg Cys Val  
 450 455 460

Cys Lys Asp Asn Val Glu Gly Phe Asn Cys Glu Arg Cys Lys Pro Gly  
 465 470 475 480

Phe Phe Asn Leu Glu Ser Ser Asn Pro Arg Gly Cys Thr Pro Cys Phe  
 485 490 495

Cys Phe Gly His Ser Ser Val Cys Thr Asn Ala Val Gly Tyr Ser Val  
 500 505 510

Tyr Ser Ile Ser Ser Thr Phe Gln Ile Asp Glu Asp Gly Trp Arg Ala  
 515 520 525

Glu Gln Arg Asp Gly Ser Glu Ala Ser Leu Glu Trp Ser Ser Glu Arg  
 530 535 540

Gln Asp Ile Ala Val Ile Ser Asp Ser Tyr Phe Pro Arg Tyr Phe Ile  
 545 550 555 560

Ala Pro Ala Lys Phe Leu Gly Lys Gln Val Leu Ser Tyr Gly Gln Asn  
 565 570 575

Leu Ser Phe Ser Phe Arg Val Asp Arg Arg Asp Thr Arg Leu Ser Ala  
 580 585 590

Glu Asp Leu Val Leu Glu Gly Ala Gly Leu Arg Val Ser Val Pro Leu  
 595 600 605

Ile Ala Gln Gly Asn Ser Tyr Pro Ser Glu Thr Thr Val Lys Tyr Val  
 610 615 620

Phe Arg Leu His Glu Ala Thr Asp Tyr Pro Trp Arg Pro Ala Leu Thr  
 625 630 635 640

Pro Phe Glu Phe Gln Lys Leu Leu Asn Asn Leu Thr Ser Ile Lys Ile  
 645 650 655

Arg Gly Thr Tyr Ser Glu Arg Ser Ala Gly Tyr Leu Asp Asp Val Thr  
 660 665 670

Leu Ala Ser Ala Arg Pro Gly Pro Gly Val Pro Ala Thr Trp Val Glu

675	680	685
Ser Cys Thr Cys Pro Val Gly Tyr Gly Gly Gln Phe Cys Glu Met Cys		
690	695	700
Leu Ser Gly Tyr Arg Arg Glu Thr Pro Asn Leu Gly Pro Tyr Ser Pro		
705	710	715
Cys Val Leu Cys Ala Cys Asn Gly His Ser Glu Thr Cys Asp Pro Glu		
	725	730
Thr Gly Val Cys Asn Cys Arg Asp Asn Thr Ala Gly Pro His Cys Glu		
	740	745
Lys Cys Ser Asp Gly Tyr Tyr Gly Asp Ser Thr Ala Gly Thr Ser Ser		
	755	760
Asp Cys Gln Pro Cys Pro Cys Pro Gly Gly Ser Ser Cys Ala Val Val		
	770	775
Pro Lys Thr Lys Glu Val Val Cys Thr Asn Cys Pro Thr Gly Thr Thr		
785	790	795
Gly Lys Arg Cys Glu Leu Cys Asp Asp Gly Tyr Phe Gly Asp Pro Leu		
	805	810
Gly Arg Asn Gly Pro Val Arg Leu Cys Arg Leu Cys Gln Cys Ser Asp		
	820	825
Asn Ile Asp Pro Asn Ala Val Gly Asn Cys Asn Arg Leu Thr Gly Glu		
	835	840
Cys Leu Lys Cys Ile Tyr Asn Thr Ala Gly Phe Tyr Cys Asp Arg Cys		
	850	855
Lys Asp Gly Phe Phe Gly Asn Pro Leu Ala Pro Asn Pro Ala Asp Lys		
865	870	875
Cys Lys Ala Cys Asn Cys Asn Pro Tyr Gly Thr Met Lys Gln Gln Ser		
	885	890
Ser Cys Asn Pro Val Thr Gly Gln Cys Glu Cys Leu Pro His Val Thr		
	900	905
		910

Gly Gln Asp Cys Gly Ala Cys Asp Pro Gly Phe Tyr Asn Leu Gln Ser  
 915 920 925

Gly Gln Gly Cys Glu Arg Cys Asp Cys His Ala Leu Gly Ser Thr Asn  
 930 935 940

Gly Gln Cys Asp Ile Arg Thr Gly Gln Cys Glu Cys Gln Pro Gly Ile  
 945 950 955 960

Thr Gly Gln His Cys Glu Arg Cys Glu Val Asn His Phe Gly Phe Gly  
 965 970 975

Pro Glu Gly Cys Lys Pro Cys Asp Cys His Pro Glu Gly Ser Leu Ser  
 980 985 990

Leu Gln Cys Lys Asp Asp Gly Arg Cys Glu Cys Arg Glu Gly Phe Val  
 995 1000 1005

Gly Asn Arg Cys Asp Gln Cys Glu Glu Asn Tyr Phe Tyr Asn Arg  
 1010 1015 1020

Ser Trp Pro Gly Cys Gln Glu Cys Pro Ala Cys Tyr Arg Leu Val  
 1025 1030 1035

Lys Asp Lys Val Ala Asp His Arg Val Lys Leu Gln Glu Leu Glu  
 1040 1045 1050

Ser Leu Ile Ala Asn Leu Gly Thr Gly Asp Glu Met Val Thr Asp  
 1055 1060 1065

Gln Ala Phe Glu Asp Arg Leu Lys Glu Ala Glu Arg Glu Val Met  
 1070 1075 1080

Asp Leu Leu Arg Glu Ala Gln Asp Val Lys Asp Val Asp Gln Asn  
 1085 1090 1095

Leu Met Asp Arg Leu Gln Arg Val Asn Asn Thr Leu Ser Ser Gln  
 1100 1105 1110

Ile Ser Arg Leu Gln Asn Ile Arg Asn Thr Ile Glu Glu Thr Gly  
 1115 1120 1125

Asn Leu Ala Glu Gln Ala Arg Ala His Val Glu Asn Thr Glu Arg  
 1130 1135 1140

Leu Ile Glu Ile Ala Ser Arg Glu Leu Glu Lys Ala Lys Val Ala  
 1145 1150 1155

Ala Ala Asn Val Ser Val Thr Gln Pro Glu Ser Thr Gly Asp Pro  
 1160 1165 1170

Asn Asn Met Thr Leu Leu Ala Glu Glu Ala Arg Lys Leu Ala Glu  
 1175 1180 1185

Arg His Lys Gln Glu Ala Asp Asp Ile Val Arg Val Ala Lys Thr  
 1190 1195 1200

Ala Asn Asp Thr Ser Thr Glu Ala Tyr Asn Leu Leu Leu Arg Thr  
 1205 1210 1215

Leu Ala Gly Glu Asn Gln Thr Ala Phe Glu Ile Glu Glu Leu Asn  
 1220 1225 1230

Arg Lys Tyr Glu Gln Ala Lys Asn Ile Ser Gln Asp Leu Glu Lys  
 1235 1240 1245

Gln Ala Ala Arg Val His Glu Glu Ala Lys Arg Ala Gly Asp Lys  
 1250 1255 1260

Ala Val Glu Ile Tyr Ala Ser Val Ala Gln Leu Ser Pro Leu Asp  
 1265 1270 1275

Ser Glu Thr Leu Glu Asn Glu Ala Asn Asn Ile Lys Met Glu Ala  
 1280 1285 1290

Glu Asn Leu Glu Gln Leu Ile Asp Gln Lys Leu Lys Asp Tyr Glu  
 1295 1300 1305

Asp Leu Arg Glu Asp Met Arg Gly Lys Glu Leu Glu Val Lys Asn  
 1310 1315 1320

Leu Leu Glu Lys Gly Lys Thr Glu Gln Gln Thr Ala Asp Gln Leu  
 1325 1330 1335

Leu Ala Arg Ala Asp Ala Ala Lys Ala Leu Ala Glu Glu Ala Ala  
 1340 1345 1350

Lys Lys Gly Arg Asp Thr Leu Gln Glu Ala Asn Asp Ile Leu Asn  
 1355 1360 1365

Asn Leu Lys Asp Phe Asp Arg Arg Val Asn Asp Asn Lys Thr Ala  
 1370 1375 1380

Ala Glu Glu Ala Leu Arg Lys Ile Pro Ala Ile Asn Gln Thr Ile  
 1385 1390 1395

Thr Glu Ala Asn Glu Lys Thr Arg Glu Ala Gln Gln Ala Leu Gly  
 1400 1405 1410

Ser Ala Ala Ala Asp Ala Thr Glu Ala Lys Asn Lys Ala His Glu  
 1415 1420 1425

Ala Glu Arg Ile Ala Ser Ala Val Gln Lys Asn Ala Thr Ser Thr  
 1430 1435 1440

Lys Ala Glu Ala Glu Arg Thr Phe Ala Glu Val Thr Asp Leu Asp  
 1445 1450 1455

Asn Glu Val Asn Asn Met Leu Lys Gln Leu Gln Glu Ala Glu Lys  
 1460 1465 1470

Glu Leu Lys Arg Lys Gln Asp Asp Ala Asp Gln Asp Met Met Met  
 1475 1480 1485

Ala Gly Met Ala Ser Gln Ala Ala Gln Glu Ala Glu Ile Asn Ala  
 1490 1495 1500

Arg Lys Ala Lys Asn Ser Val Thr Ser Leu Leu Ser Ile Ile Asn  
 1505 1510 1515

Asp Leu Leu Glu Gln Leu Gly Gln Leu Asp Thr Val Asp Leu Asn  
 1520 1525 1530

Lys Leu Asn Glu Ile Glu Gly Thr Leu Asn Lys Ala Lys Asp Glu  
 1535 1540 1545

Met Lys Val Ser Asp Leu Asp Arg Lys Val Ser Asp Leu Glu Asn

1550                                      1555                                      1560  
 Glu Ala Lys Lys Gln Glu Ala Ala Ile Met Asp Tyr Asn Arg Asp  
     1565                                      1570                                      1575  
  
 Ile Glu Glu Ile Met Lys Asp Ile Arg Asn Leu Glu Asp Ile Arg  
     1580                                      1585                                      1590  
  
 Lys Thr Leu Pro Ser Gly Cys Phe Asn Thr Pro Ser Ile Glu Lys  
     1595                                      1600                                      1605  
  
 Pro  
  
 <210> 186  
 <211> 1408  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 186  
  
 Met Lys Ala Pro Ala Val Leu Ala Pro Gly Ile Leu Val Leu Leu Phe  
     1                                      5                                      10                                      15  
  
 Thr Leu Val Gln Arg Ser Asn Gly Glu Cys Lys Glu Ala Leu Ala Lys  
             20                                      25                                      30  
  
 Ser Glu Met Asn Val Asn Met Lys Tyr Gln Leu Pro Asn Phe Thr Ala  
             35                                      40                                      45  
  
 Glu Thr Pro Ile Gln Asn Val Ile Leu His Glu His His Ile Phe Leu  
     50                                      55                                      60  
  
 Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn Glu Glu Asp Leu Gln Lys  
     65                                      70                                      75                                      80  
  
 Val Ala Glu Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe  
             85                                      90                                      95  
  
 Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp  
             100                                      105                                      110  
  
 Lys Asp Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp  
     115                                      120                                      125

Gln Leu Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His  
 130 135 140

Val Phe Pro His Asn His Thr Ala Asp Ile Gln Ser Glu Val His Cys  
 145 150 155 160

Ile Phe Ser Pro Gln Ile Glu Glu Pro Ser Gln Cys Pro Asp Cys Val  
 165 170 175

Val Ser Ala Leu Gly Ala Lys Val Leu Ser Ser Val Lys Asp Arg Phe  
 180 185 190

Ile Asn Phe Phe Val Gly Asn Thr Ile Asn Ser Ser Tyr Phe Pro Asp  
 195 200 205

His Pro Leu His Ser Ile Ser Val Arg Arg Leu Lys Glu Thr Lys Asp  
 210 215 220

Gly Phe Met Phe Leu Thr Asp Gln Ser Tyr Ile Asp Val Leu Pro Glu  
 225 230 235 240

Phe Arg Asp Ser Tyr Pro Ile Lys Tyr Val His Ala Phe Glu Ser Asn  
 245 250 255

Asn Phe Ile Tyr Phe Leu Thr Val Gln Arg Glu Thr Leu Asp Ala Gln  
 260 265 270

Thr Phe His Thr Arg Ile Ile Arg Phe Cys Ser Ile Asn Ser Gly Leu  
 275 280 285

His Ser Tyr Met Glu Met Pro Leu Glu Cys Ile Leu Thr Glu Lys Arg  
 290 295 300

Lys Lys Arg Ser Thr Lys Lys Glu Val Phe Asn Ile Leu Gln Ala Ala  
 305 310 315 320

Tyr Val Ser Lys Pro Gly Ala Gln Leu Ala Arg Gln Ile Gly Ala Ser  
 325 330 335

Leu Asn Asp Asp Ile Leu Phe Gly Val Phe Ala Gln Ser Lys Pro Asp  
 340 345 350

Ser Ala Glu Pro Met Asp Arg Ser Ala Met Cys Ala Phe Pro Ile Lys  
 355 360 365  
 Tyr Val Asn Asp Phe Phe Asn Lys Ile Val Asn Lys Asn Asn Val Arg  
 370 375 380  
 Cys Leu Gln His Phe Tyr Gly Pro Asn His Glu His Cys Phe Asn Arg  
 385 390 395 400  
 Thr Leu Leu Arg Asn Ser Ser Gly Cys Glu Ala Arg Arg Asp Glu Tyr  
 405 410 415  
 Arg Thr Glu Phe Thr Thr Ala Leu Gln Arg Val Asp Leu Phe Met Gly  
 420 425 430  
 Gln Phe Ser Glu Val Leu Leu Thr Ser Ile Ser Thr Phe Ile Lys Gly  
 435 440 445  
 Asp Leu Thr Ile Ala Asn Leu Gly Thr Ser Glu Gly Arg Phe Met Gln  
 450 455 460  
 Val Val Val Ser Arg Ser Gly Pro Ser Thr Pro His Val Asn Phe Leu  
 465 470 475 480  
 Leu Asp Ser His Pro Val Ser Pro Glu Val Ile Val Glu His Thr Leu  
 485 490 495  
 Asn Gln Asn Gly Tyr Thr Leu Val Ile Thr Gly Lys Lys Ile Thr Lys  
 500 505 510  
 Ile Pro Leu Asn Gly Leu Gly Cys Arg His Phe Gln Ser Cys Ser Gln  
 515 520 525  
 Cys Leu Ser Ala Pro Pro Phe Val Gln Cys Gly Trp Cys His Asp Lys  
 530 535 540  
 Cys Val Arg Ser Glu Glu Cys Leu Ser Gly Thr Trp Thr Gln Gln Ile  
 545 550 555 560  
 Cys Leu Pro Ala Ile Tyr Lys Val Phe Pro Asn Ser Ala Pro Leu Glu  
 565 570 575  
 Gly Gly Thr Arg Leu Thr Ile Cys Gly Trp Asp Phe Gly Phe Arg Arg



580

585

590

Asn Asn Lys Phe Asp Leu Lys Lys Thr Arg Val Leu Leu Gly Asn Glu  
 595 600 605

Ser Cys Thr Leu Thr Leu Ser Glu Ser Thr Met Asn Thr Leu Lys Cys  
 610 615 620

Thr Val Gly Pro Ala Met Asn Lys His Phe Asn Met Ser Ile Ile Ile  
 625 630 635 640

Ser Asn Gly His Gly Thr Thr Gln Tyr Ser Thr Phe Ser Tyr Val Asp  
 645 650 655

Pro Val Ile Thr Ser Ile Ser Pro Lys Tyr Gly Pro Met Ala Gly Gly  
 660 665 670

Thr Leu Leu Thr Leu Thr Gly Asn Tyr Leu Asn Ser Gly Asn Ser Arg  
 675 680 685

His Ile Ser Ile Gly Gly Lys Thr Cys Thr Leu Lys Ser Val Ser Asn  
 690 695 700

Ser Ile Leu Glu Cys Tyr Thr Pro Ala Gln Thr Ile Ser Thr Glu Phe  
 705 710 715 720

Ala Val Lys Leu Lys Ile Asp Leu Ala Asn Arg Glu Thr Ser Ile Phe  
 725 730 735

Ser Tyr Arg Glu Asp Pro Ile Val Tyr Glu Ile His Pro Thr Lys Ser  
 740 745 750

Phe Ile Ser Thr Trp Trp Lys Glu Pro Leu Asn Ile Val Ser Phe Leu  
 755 760 765

Phe Cys Phe Ala Ser Gly Gly Ser Thr Ile Thr Gly Val Gly Lys Asn  
 770 775 780

Leu Asn Ser Val Ser Val Pro Arg Met Val Ile Asn Val His Glu Ala  
 785 790 795 800

Gly Arg Asn Phe Thr Val Ala Cys Gln His Arg Ser Asn Ser Glu Ile  
 805 810 815

Ile Cys Cys Thr Thr Pro Ser Leu Gln Gln Leu Asn Leu Gln Leu Pro  
 820 825 830

Leu Lys Thr Lys Ala Phe Phe Met Leu Asp Gly Ile Leu Ser Lys Tyr  
 835 840 845

Phe Asp Leu Ile Tyr Val His Asn Pro Val Phe Lys Pro Phe Glu Lys  
 850 855 860

Pro Val Met Ile Ser Met Gly Asn Glu Asn Val Leu Glu Ile Lys Gly  
 865 870 875 880

Asn Asp Ile Asp Pro Glu Ala Val Lys Gly Glu Val Leu Lys Val Gly  
 885 890 895

Asn Lys Ser Cys Glu Asn Ile His Leu His Ser Glu Ala Val Leu Cys  
 900 905 910

Thr Val Pro Asn Asp Leu Leu Lys Leu Asn Ser Glu Leu Asn Ile Glu  
 915 920 925

Trp Lys Gln Ala Ile Ser Ser Thr Val Leu Gly Lys Val Ile Val Gln  
 930 935 940

Pro Asp Gln Asn Phe Thr Gly Leu Ile Ala Gly Val Val Ser Ile Ser  
 945 950 955 960

Thr Ala Leu Leu Leu Leu Leu Gly Phe Phe Leu Trp Leu Lys Lys Arg  
 965 970 975

Lys Gln Ile Lys Asp Leu Gly Ser Glu Leu Val Arg Tyr Asp Ala Arg  
 980 985 990

Val His Thr Pro His Leu Asp Arg Leu Val Ser Ala Arg Ser Val Ser  
 995 1000 1005

Pro Thr Thr Glu Met Val Ser Asn Glu Ser Val Asp Tyr Arg Ala  
 1010 1015 1020

Thr Phe Pro Glu Asp Gln Phe Pro Asn Ser Ser Gln Asn Gly Ser  
 1025 1030 1035

Cys Arg Gln Val Gln Tyr Pro Leu Thr Asp Met Ser Pro Ile Leu  
 1040 1045 1050  
 Thr Ser Gly Asp Ser Asp Ile Ser Ser Pro Leu Leu Gln Asn Thr  
 1055 1060 1065  
 Val His Ile Asp Leu Ser Ala Leu Asn Pro Glu Leu Val Gln Ala  
 1070 1075 1080  
 Val Gln His Val Val Ile Gly Pro Ser Ser Leu Ile Val His Phe  
 1085 1090 1095  
 Asn Glu Val Ile Gly Arg Gly His Phe Gly Cys Val Tyr His Gly  
 1100 1105 1110  
 Thr Leu Leu Asp Asn Asp Gly Lys Lys Ile His Cys Ala Val Lys  
 1115 1120 1125  
 Ser Leu Asn Arg Ile Thr Asp Ile Gly Glu Val Ser Gln Phe Leu  
 1130 1135 1140  
 Thr Glu Gly Ile Ile Met Lys Asp Phe Ser His Pro Asn Val Leu  
 1145 1150 1155  
 Ser Leu Leu Gly Ile Cys Leu Arg Ser Glu Gly Ser Pro Leu Val  
 1160 1165 1170  
 Val Leu Pro Tyr Met Lys His Gly Asp Leu Arg Asn Phe Ile Arg  
 1175 1180 1185  
 Asn Glu Thr His Asn Pro Thr Val Lys Asp Leu Ile Gly Phe Gly  
 1190 1195 1200  
 Leu Gln Val Ala Lys Ala Met Lys Tyr Leu Ala Ser Lys Lys Phe  
 1205 1210 1215  
 Val His Arg Asp Leu Ala Ala Arg Asn Cys Met Leu Asp Glu Lys  
 1220 1225 1230  
 Phe Thr Val Lys Val Ala Asp Phe Gly Leu Ala Arg Asp Met Tyr  
 1235 1240 1245

Asp Lys Glu Tyr Tyr Ser Val His Asn Lys Thr Gly Ala Lys Leu  
1250 1255 1260

Pro Val Lys Trp Met Ala Leu Glu Ser Leu Gln Thr Gln Lys Phe  
1265 1270 1275

Thr Thr Lys Ser Asp Val Trp Ser Phe Gly Val Val Leu Trp Glu  
1280 1285 1290

Leu Met Thr Arg Gly Ala Pro Pro Tyr Pro Asp Val Asn Thr Phe  
1295 1300 1305

Asp Ile Thr Val Tyr Leu Leu Gln Gly Arg Arg Leu Leu Gln Pro  
1310 1315 1320

Glu Tyr Cys Pro Asp Pro Leu Tyr Glu Val Met Leu Lys Cys Trp  
1325 1330 1335

His Pro Lys Ala Glu Met Arg Pro Ser Phe Ser Glu Leu Val Ser  
1340 1345 1350

Arg Ile Ser Ala Ile Phe Ser Thr Phe Ile Gly Glu His Tyr Val  
1355 1360 1365

His Val Asn Ala Thr Tyr Val Asn Val Lys Cys Val Ala Pro Tyr  
1370 1375 1380

Pro Ser Leu Leu Ser Ser Glu Asp Asn Ala Asp Asp Glu Val Asp  
1385 1390 1395

Thr Arg Pro Ala Ser Phe Trp Glu Thr Ser  
1400 1405

<210> 187  
<211> 577  
<212> PRT  
<213> Homo sapiens

<400> 187

Met Pro Lys Thr Ile Ser Val Arg Val Thr Thr Met Asp Ala Glu Leu  
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Glu Phe Ala Ile Gln Pro Asn Thr Thr Gly Lys Gln Leu Phe Asp Gln  
20 25 30

Val Val Lys Thr Ile Gly Leu Arg Glu Val Trp Phe Phe Gly Leu Gln  
 35 40 45

Tyr Gln Asp Thr Lys Gly Phe Ser Thr Trp Leu Lys Leu Asn Lys Lys  
 50 55 60

Val Thr Ala Gln Asp Val Arg Lys Glu Ser Pro Leu Leu Phe Lys Phe  
 65 70 75 80

Arg Ala Lys Phe Tyr Pro Glu Asp Val Ser Glu Glu Leu Ile Gln Asp  
 85 90 95

Ile Thr Gln Arg Leu Phe Phe Leu Gln Val Lys Glu Gly Ile Leu Asn  
 100 105 110

Asp Asp Ile Tyr Cys Pro Pro Glu Thr Ala Val Leu Leu Ala Ser Tyr  
 115 120 125

Ala Val Gln Ser Lys Tyr Gly Asp Phe Asn Lys Glu Val His Lys Ser  
 130 135 140

Gly Tyr Leu Ala Gly Asp Lys Leu Leu Pro Gln Arg Val Leu Glu Gln  
 145 150 155 160

His Lys Leu Asn Lys Asp Gln Trp Glu Glu Arg Ile Gln Val Trp His  
 165 170 175

Glu Glu His Arg Gly Met Leu Arg Glu Asp Ala Val Leu Glu Tyr Leu  
 180 185 190

Lys Ile Ala Gln Asp Leu Glu Met Tyr Gly Val Asn Tyr Phe Ser Ile  
 195 200 205

Lys Asn Lys Lys Gly Ser Glu Leu Trp Leu Gly Val Asp Ala Leu Gly  
 210 215 220

Leu Asn Ile Tyr Glu Gln Asn Asp Arg Leu Thr Pro Lys Ile Gly Phe  
 225 230 235 240

Pro Trp Ser Glu Ile Arg Asn Ile Ser Phe Asn Asp Lys Lys Phe Val  
 245 250 255

Ile Lys Pro Ile Asp Lys Lys Ala Pro Asp Phe Val Phe Tyr Ala Pro  
 260 265 270

Arg Leu Arg Ile Asn Lys Arg Ile Leu Ala Leu Cys Met Gly Asn His  
 275 280 285

Glu Leu Tyr Met Arg Arg Arg Lys Pro Asp Thr Ile Glu Val Gln Gln  
 290 295 300

Met Lys Ala Gln Ala Arg Glu Glu Lys His Gln Lys Gln Met Glu Arg  
 305 310 315 320

Ala Met Leu Glu Asn Glu Lys Lys Lys Arg Glu Met Ala Glu Lys Glu  
 325 330 335

Lys Glu Lys Ile Glu Arg Glu Lys Glu Glu Leu Met Glu Arg Leu Lys  
 340 345 350

Gln Ile Glu Glu Gln Thr Lys Lys Ala Gln Gln Glu Leu Glu Glu Gln  
 355 360 365

Thr Arg Arg Ala Leu Glu Leu Glu Gln Glu Arg Lys Arg Ala Gln Ser  
 370 375 380

Glu Ala Glu Lys Leu Ala Lys Glu Arg Gln Glu Ala Glu Glu Ala Lys  
 385 390 395 400

Glu Ala Leu Leu Gln Ala Ser Arg Asp Gln Lys Lys Thr Gln Glu Gln  
 405 410 415

Leu Ala Leu Glu Met Ala Glu Leu Thr Ala Arg Ile Ser Gln Leu Glu  
 420 425 430

Met Ala Arg Gln Lys Lys Glu Ser Glu Ala Val Glu Trp Gln Gln Lys  
 435 440 445

Ala Gln Met Val Gln Glu Asp Leu Glu Lys Thr Arg Ala Glu Leu Lys  
 450 455 460

Thr Ala Met Ser Thr Pro His Val Ala Glu Pro Ala Glu Asn Glu Gln  
 465 470 475 480

Asp Glu Gln Asp Glu Asn Gly Ala Glu Ala Ser Ala Asp Leu Arg Ala  
 485 490 495

Asp Ala Met Ala Lys Asp Arg Ser Glu Glu Glu Arg Thr Thr Glu Ala  
 500 505 510

Glu Lys Asn Glu Arg Val Gln Lys His Leu Lys Ala Leu Thr Ser Glu  
 515 520 525

Leu Ala Asn Ala Arg Asp Glu Ser Lys Lys Thr Ala Asn Asp Met Ile  
 530 535 540

His Ala Glu Asn Met Arg Leu Gly Arg Asp Lys Tyr Lys Thr Leu Arg  
 545 550 555 560

Gln Ile Arg Gln Gly Asn Thr Lys Gln Arg Ile Asp Glu Phe Glu Ser  
 565 570 575

Met

<210> 188  
 <211> 2058  
 <212> PRT  
 <213> Homo sapiens

<400> 188

Met Asp Asn Phe Phe Thr Glu Gly Thr Arg Val Trp Leu Arg Glu Asn  
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Gly Gln His Phe Pro Ser Thr Val Asn Ser Cys Ala Glu Gly Ile Val  
 20 25 30

Val Phe Arg Thr Asp Tyr Gly Gln Val Phe Thr Tyr Lys Gln Ser Thr  
 35 40 45

Ile Thr His Gln Lys Val Thr Ala Met His Pro Thr Asn Glu Glu Gly  
 50 55 60

Val Asp Asp Met Ala Ser Leu Thr Glu Leu His Gly Gly Ser Ile Met  
 65 70 75 80

Tyr Asn Leu Phe Gln Arg Tyr Lys Arg Asn Gln Ile Tyr Thr Tyr Ile  
 85 90 95

Gly Ser Ile Leu Ala Ser Val Asn Pro Tyr Gln Pro Ile Ala Gly Leu  
 100 105 110

Tyr Glu Pro Ala Thr Met Glu Gln Tyr Ser Arg Arg His Leu Gly Glu  
 115 120 125

Leu Pro Pro His Ile Phe Ala Ile Ala Asn Glu Cys Tyr Arg Cys Leu  
 130 135 140

Trp Lys Arg Tyr Asp Asn Gln Cys Ile Leu Ile Ser Gly Glu Ser Gly  
 145 150 155 160

Ala Gly Lys Thr Glu Ser Thr Lys Leu Ile Leu Lys Phe Leu Ser Val  
 165 170 175

Ile Ser Gln Gln Ser Leu Glu Leu Ser Leu Lys Glu Lys Thr Ser Cys  
 180 185 190

Val Glu Arg Ala Ile Leu Glu Ser Ser Pro Ile Met Glu Ala Phe Gly  
 195 200 205

Asn Ala Lys Thr Val Tyr Asn Asn Asn Ser Ser Arg Phe Gly Lys Phe  
 210 215 220

Val Gln Leu Asn Ile Cys Gln Lys Gly Asn Ile Gln Gly Gly Arg Ile  
 225 230 235 240

Val Asp Tyr Leu Leu Glu Lys Asn Arg Val Val Arg Gln Asn Pro Gly  
 245 250 255

Glu Arg Asn Tyr His Ile Phe Tyr Ala Leu Leu Ala Gly Leu Glu His  
 260 265 270

Glu Glu Arg Glu Glu Phe Tyr Leu Ser Thr Pro Glu Asn Tyr His Tyr  
 275 280 285

Leu Asn Gln Ser Gly Cys Val Glu Asp Lys Thr Ile Ser Asp Gln Glu  
 290 295 300

Ser Phe Arg Glu Val Ile Thr Ala Met Asp Val Met Gln Phe Ser Lys  
 305 310 315 320



Glu Glu Val Arg Glu Val Ser Arg Leu Leu Ala Gly Ile Leu His Leu  
 325 330 335

Gly Asn Ile Glu Phe Ile Thr Ala Gly Gly Ala Gln Val Ser Phe Lys  
 340 345 350

Thr Ala Leu Gly Arg Ser Ala Glu Leu Leu Gly Leu Asp Pro Thr Gln  
 355 360 365

Leu Thr Asp Ala Leu Thr Gln Arg Ser Met Phe Leu Arg Gly Glu Glu  
 370 375 380

Ile Leu Thr Pro Leu Asn Val Gln Gln Ala Val Asp Ser Arg Asp Ser  
 385 390 395 400

Leu Ala Met Ala Leu Tyr Ala Cys Cys Phe Glu Trp Val Ile Lys Lys  
 405 410 415

Ile Asn Ser Arg Ile Lys Gly Asn Glu Asp Phe Lys Ser Ile Gly Ile  
 420 425 430

Leu Asp Ile Phe Gly Phe Glu Asn Phe Glu Val Asn His Phe Glu Gln  
 435 440 445

Phe Asn Ile Asn Tyr Ala Asn Glu Lys Leu Gln Glu Tyr Phe Asn Lys  
 450 455 460

His Ile Phe Ser Leu Glu Gln Leu Glu Tyr Ser Arg Glu Gly Leu Val  
 465 470 475 480

Trp Glu Asp Ile Asp Trp Ile Asp Asn Gly Glu Cys Leu Asp Leu Ile  
 485 490 495

Glu Lys Lys Leu Gly Leu Leu Ala Leu Ile Asn Glu Glu Ser His Phe  
 500 505 510

Pro Gln Ala Thr Asp Ser Thr Leu Leu Glu Lys Leu His Ser Gln His  
 515 520 525

Ala Asn Asn His Phe Tyr Val Lys Pro Arg Val Ala Val Asn Asn Phe  
 530 535 540

Gly Val Lys His Tyr Ala Gly Glu Val Gln Tyr Asp Val Arg Gly Ile  
 545 550 555 560

Leu Glu Lys Asn Arg Asp Thr Phe Arg Asp Asp Leu Leu Asn Leu Leu  
 565 570 575

Arg Glu Ser Arg Phe Asp Phe Ile Tyr Asp Leu Phe Glu His Val Ser  
 580 585 590

Ser Arg Asn Asn Gln Asp Thr Leu Lys Cys Gly Ser Lys His Arg Arg  
 595 600 605

Pro Thr Val Ser Ser Gln Phe Lys Asp Ser Leu His Ser Leu Met Ala  
 610 615 620

Thr Leu Ser Ser Ser Asn Pro Phe Phe Val Arg Cys Ile Lys Pro Asn  
 625 630 635 640

Met Gln Lys Met Pro Asp Gln Phe Asp Gln Ala Val Val Leu Asn Gln  
 645 650 655

Leu Arg Tyr Ser Gly Met Leu Glu Thr Val Arg Ile Arg Lys Ala Gly  
 660 665 670

Tyr Ala Val Arg Arg Pro Phe Gln Asp Phe Tyr Lys Arg Tyr Lys Val  
 675 680 685

Leu Met Arg Asn Leu Ala Leu Pro Glu Asp Val Arg Gly Lys Cys Thr  
 690 695 700

Ser Leu Leu Gln Leu Tyr Asp Ala Ser Asn Ser Glu Trp Gln Leu Gly  
 705 710 715 720

Lys Thr Lys Val Phe Leu Arg Glu Ser Leu Glu Gln Lys Leu Glu Lys  
 725 730 735

Arg Arg Glu Glu Glu Val Ser His Ala Ala Met Val Ile Arg Ala His  
 740 745 750

Val Leu Gly Phe Leu Ala Arg Lys Gln Tyr Arg Lys Val Leu Tyr Cys  
 755 760 765

Val Val Ile Ile Gln Lys Asn Tyr Arg Ala Phe Leu Leu Arg Arg Arg

770

775

780

Phe Leu His Leu Lys Lys Ala Ala Ile Val Phe Gln Lys Gln Leu Arg  
 785 790 795 800

Gly Gln Ile Ala Arg Arg Val Tyr Arg Gln Leu Leu Ala Glu Lys Arg  
 805 810 815

Glu Gln Glu Glu Lys Lys Lys Gln Glu Glu Glu Glu Lys Lys Lys Arg  
 820 825 830

Glu Glu Glu Glu Arg Glu Arg Glu Arg Glu Arg Arg Glu Ala Glu Leu  
 835 840 845

Arg Ala Gln Gln Glu Glu Glu Thr Arg Lys Gln Gln Glu Leu Glu Ala  
 850 855 860

Leu Gln Lys Ser Gln Lys Glu Ala Glu Leu Thr Arg Glu Leu Glu Lys  
 865 870 875 880

Gln Lys Glu Asn Lys Gln Val Glu Glu Ile Leu Arg Leu Glu Lys Glu  
 885 890 895

Ile Glu Asp Leu Gln Arg Met Lys Glu Gln Gln Glu Leu Ser Leu Thr  
 900 905 910

Glu Ala Ser Leu Gln Lys Leu Gln Glu Arg Arg Asp Gln Glu Leu Arg  
 915 920 925

Arg Leu Glu Glu Glu Ala Cys Arg Ala Ala Gln Glu Phe Leu Glu Ser  
 930 935 940

Leu Asn Phe Asp Glu Ile Asp Glu Cys Val Arg Asn Ile Glu Arg Ser  
 945 950 955 960

Leu Ser Val Gly Ser Glu Phe Ser Ser Glu Leu Ala Glu Ser Ala Cys  
 965 970 975

Glu Glu Lys Pro Asn Phe Asn Phe Ser Gln Pro Tyr Pro Glu Glu Glu  
 980 985 990

Val Asp Glu Gly Phe Glu Ala Asp Asp Asp Ala Phe Lys Asp Ser Pro  
 995 1000 1005

Asn Pro	Ser Glu His Gly His	Ser Asp Gln Arg Thr	Ser Gly Ile
1010	1015	1020	
Arg Thr	Ser Asp Asp Ser Ser	Glu Glu Asp Pro Tyr	Met Asn Asp
1025	1030	1035	
Thr Val	Val Pro Thr Ser Pro	Ser Ala Asp Ser Thr	Val Leu Leu
1040	1045	1050	
Ala Pro	Ser Val Gln Asp Ser	Gly Ser Leu His Asn	Ser Ser Ser
1055	1060	1065	
Gly Glu	Ser Thr Tyr Cys Met	Pro Gln Asn Ala Gly	Asp Leu Pro
1070	1075	1080	
Ser Pro	Asp Gly Asp Tyr Asp	Tyr Asp Gln Asp Asp	Tyr Glu Asp
1085	1090	1095	
Gly Ala	Ile Thr Ser Gly Ser	Ser Val Thr Phe Ser	Asn Ser Tyr
1100	1105	1110	
Gly Ser	Gln Trp Ser Pro Asp	Tyr Arg Cys Ser Val	Gly Thr Tyr
1115	1120	1125	
Asn Ser	Ser Gly Ala Tyr Arg	Phe Ser Ser Glu Gly	Ala Gln Ser
1130	1135	1140	
Ser Phe	Glu Asp Ser Glu Glu	Asp Phe Asp Ser Arg	Phe Asp Thr
1145	1150	1155	
Asp Asp	Glu Leu Ser Tyr Arg	Arg Asp Ser Val Tyr	Ser Cys Val
1160	1165	1170	
Thr Leu	Pro Tyr Phe His Ser	Phe Leu Tyr Met Lys	Gly Gly Leu
1175	1180	1185	
Met Asn	Ser Trp Lys Arg Arg	Trp Cys Val Leu Lys	Asp Glu Thr
1190	1195	1200	
Phe Leu	Trp Phe Arg Ser Lys	Gln Glu Ala Leu Lys	Gln Gly Trp
1205	1210	1215	

Leu His Lys Lys Gly Gly Gly Ser Ser Thr Leu Ser Arg Arg Asn  
 1220 1225 1230  
 Trp Lys Lys Arg Trp Phe Val Leu Arg Gln Ser Lys Leu Met Tyr  
 1235 1240 1245  
 Phe Glu Asn Asp Ser Glu Glu Lys Leu Lys Gly Thr Val Glu Val  
 1250 1255 1260  
 Arg Thr Ala Lys Glu Ile Ile Asp Asn Thr Thr Lys Glu Asn Gly  
 1265 1270 1275  
 Ile Asp Ile Ile Met Ala Asp Arg Thr Phe His Leu Ile Ala Glu  
 1280 1285 1290  
 Ser Pro Glu Asp Ala Ser Gln Trp Phe Ser Val Leu Ser Gln Val  
 1295 1300 1305  
 His Ala Ser Thr Asp Gln Glu Ile Gln Glu Met His Asp Glu Gln  
 1310 1315 1320  
 Ala Asn Pro Gln Asn Ala Val Gly Thr Leu Asp Val Gly Leu Ile  
 1325 1330 1335  
 Asp Ser Val Cys Ala Ser Asp Ser Pro Asp Arg Pro Asn Ser Phe  
 1340 1345 1350  
 Val Ile Ile Thr Ala Asn Arg Val Leu His Cys Asn Ala Asp Thr  
 1355 1360 1365  
 Pro Glu Glu Met His His Trp Ile Thr Leu Leu Gln Arg Ser Lys  
 1370 1375 1380  
 Gly Asp Thr Arg Val Glu Gly Gln Glu Phe Ile Val Arg Gly Trp  
 1385 1390 1395  
 Leu His Lys Glu Val Lys Asn Ser Pro Lys Met Ser Ser Leu Lys  
 1400 1405 1410  
 Leu Lys Lys Arg Trp Phe Val Leu Thr His Asn Ser Leu Asp Tyr  
 1415 1420 1425

Tyr Lys Ser Ser Glu Lys Asn Ala Leu Lys Leu Gly Thr Leu Val  
 1430 1435 1440  
 Leu Asn Ser Leu Cys Ser Val Val Pro Pro Asp Glu Lys Ile Phe  
 1445 1450 1455  
 Lys Glu Thr Gly Tyr Trp Asn Val Thr Val Tyr Gly Arg Lys His  
 1460 1465 1470  
 Cys Tyr Arg Leu Tyr Thr Lys Leu Leu Asn Glu Ala Thr Arg Trp  
 1475 1480 1485  
 Ser Ser Ala Ile Gln Asn Val Thr Asp Thr Lys Ala Pro Ile Asp  
 1490 1495 1500  
 Thr Pro Thr Gln Gln Leu Ile Gln Asp Ile Lys Glu Asn Cys Leu  
 1505 1510 1515  
 Asn Ser Asp Val Val Glu Gln Ile Tyr Lys Arg Asn Pro Ile Leu  
 1520 1525 1530  
 Arg Tyr Thr His His Pro Leu His Ser Pro Leu Leu Pro Leu Pro  
 1535 1540 1545  
 Tyr Gly Asp Ile Asn Leu Asn Leu Leu Lys Asp Lys Gly Tyr Thr  
 1550 1555 1560  
 Thr Leu Gln Asp Glu Ala Ile Lys Ile Phe Asn Ser Leu Gln Gln  
 1565 1570 1575  
 Leu Glu Ser Met Ser Asp Pro Ile Pro Ile Ile Gln Gly Ile Leu  
 1580 1585 1590  
 Gln Thr Gly His Asp Leu Arg Pro Leu Arg Asp Glu Leu Tyr Cys  
 1595 1600 1605  
 Gln Leu Ile Lys Gln Thr Asn Lys Val Pro His Pro Gly Ser Val  
 1610 1615 1620  
 Gly Asn Leu Tyr Ser Trp Gln Ile Leu Thr Cys Leu Ser Cys Thr  
 1625 1630 1635  
 Phe Leu Pro Ser Arg Gly Ile Leu Lys Tyr Leu Lys Phe His Leu

1640		1645		1650
Lys Arg Ile Arg Glu Gln Phe Pro Gly Thr Glu Met Glu Lys Tyr				
1655		1660		1665
Ala Leu Phe Thr Tyr Glu Ser Leu Lys Lys Thr Lys Cys Arg Glu				
1670		1675		1680
Phe Val Pro Ser Arg Asp Glu Ile Glu Ala Leu Ile His Arg Gln				
1685		1690		1695
Glu Met Thr Ser Thr Val Tyr Cys His Gly Gly Gly Ser Cys Lys				
1700		1705		1710
Ile Thr Ile Asn Ser His Thr Thr Ala Gly Glu Val Val Glu Lys				
1715		1720		1725
Leu Ile Arg Gly Leu Ala Met Glu Asp Ser Arg Asn Met Phe Ala				
1730		1735		1740
Leu Phe Glu Tyr Asn Gly His Val Asp Lys Ala Ile Glu Ser Arg				
1745		1750		1755
Thr Val Val Ala Asp Val Leu Ala Lys Phe Glu Lys Leu Ala Ala				
1760		1765		1770
Thr Ser Glu Val Gly Asp Leu Pro Trp Lys Phe Tyr Phe Lys Leu				
1775		1780		1785
Tyr Cys Phe Leu Asp Thr Asp Asn Val Pro Lys Asp Ser Val Glu				
1790		1795		1800
Phe Ala Phe Met Phe Glu Gln Ala His Glu Ala Val Ile His Gly				
1805		1810		1815
His His Pro Ala Pro Glu Glu Asn Leu Gln Val Leu Ala Ala Leu				
1820		1825		1830
Arg Leu Gln Tyr Leu Gln Gly Asp Tyr Thr Leu His Ala Ala Ile				
1835		1840		1845
Pro Pro Leu Glu Glu Val Tyr Ser Leu Gln Arg Leu Lys Ala Arg				
1850		1855		1860

Ile Ser Gln Ser Thr Lys Thr Phe Thr Pro Cys Glu Arg Leu Glu  
 1865 1870 1875  
  
 Lys Arg Arg Thr Ser Phe Leu Glu Gly Thr Leu Arg Arg Ser Phe  
 1880 1885 1890  
  
 Arg Thr Gly Ser Val Val Arg Gln Lys Val Glu Glu Glu Gln Met  
 1895 1900 1905  
  
 Leu Asp Met Trp Ile Lys Glu Glu Val Ser Ser Ala Arg Ala Ser  
 1910 1915 1920  
  
 Ile Ile Asp Lys Trp Arg Lys Phe Gln Gly Met Asn Gln Glu Gln  
 1925 1930 1935  
  
 Ala Met Ala Lys Tyr Met Ala Leu Ile Lys Glu Trp Pro Gly Tyr  
 1940 1945 1950  
  
 Gly Ser Thr Leu Phe Asp Val Glu Cys Lys Glu Gly Gly Phe Pro  
 1955 1960 1965  
  
 Gln Glu Leu Trp Leu Gly Val Ser Ala Asp Ala Val Ser Val Tyr  
 1970 1975 1980  
  
 Lys Arg Gly Glu Gly Arg Pro Leu Glu Val Phe Gln Tyr Glu His  
 1985 1990 1995  
  
 Ile Leu Ser Phe Gly Ala Pro Leu Ala Asn Thr Tyr Lys Ile Val  
 2000 2005 2010  
  
 Val Asp Glu Arg Glu Leu Leu Phe Glu Thr Ser Glu Val Val Asp  
 2015 2020 2025  
  
 Val Ala Lys Leu Met Lys Ala Tyr Ile Ser Met Ile Val Lys Lys  
 2030 2035 2040  
  
 Arg Tyr Ser Thr Thr Arg Ser Ala Ser Ser Gln Gly Ser Ser Arg  
 2045 2050 2055  
  
  
 <210> 189  
 <211> 562  
 <212> PRT



&lt;213&gt; Homo sapiens

&lt;400&gt; 189

Met Val Lys Ile Val Thr Val Lys Thr Gln Ala Tyr Gln Asp Gln Lys  
 1 5 10 15

Pro Gly Thr Ser Gly Leu Arg Lys Arg Val Lys Val Phe Gln Ser Ser  
 20 25 30

Ala Asn Tyr Ala Glu Asn Phe Ile Gln Ser Ile Ile Ser Thr Val Glu  
 35 40 45

Pro Ala Gln Arg Gln Glu Ala Thr Leu Val Val Gly Gly Asp Gly Arg  
 50 55 60

Phe Tyr Met Lys Glu Ala Ile Gln Leu Ile Ala Arg Ile Ala Ala Ala  
 65 70 75 80

Asn Gly Ile Gly Arg Leu Val Ile Gly Gln Asn Gly Ile Leu Ser Thr  
 85 90 95

Pro Ala Val Ser Cys Ile Ile Arg Lys Ile Lys Ala Ile Gly Gly Ile  
 100 105 110

Ile Leu Thr Ala Ser His Asn Pro Gly Gly Pro Asn Gly Asp Phe Gly  
 115 120 125

Ile Lys Phe Asn Ile Ser Asn Gly Gly Pro Ala Pro Glu Ala Ile Thr  
 130 135 140

Asp Lys Ile Phe Gln Ile Ser Lys Thr Ile Glu Glu Tyr Ala Val Cys  
 145 150 155 160

Pro Asp Leu Lys Val Asp Leu Gly Val Leu Gly Lys Gln Gln Phe Asp  
 165 170 175

Leu Glu Asn Lys Phe Lys Pro Phe Thr Val Glu Ile Val Asp Ser Val  
 180 185 190

Glu Ala Tyr Ala Thr Met Leu Arg Ser Ile Phe Asp Phe Ser Ala Leu  
 195 200 205

Lys Glu Leu Leu Ser Gly Pro Asn Arg Leu Lys Ile Cys Ile Asp Ala

210		215		220
Met His Gly Val Val Gly Pro Tyr Val Lys Lys Ile Leu Cys Glu Glu				
225		230		235 240
Leu Gly Ala Pro Ala Asn Ser Ala Val Asn Cys Val Pro Leu Glu Asp				
	245		250	255
Phe Gly Gly His His Pro Asp Pro Asn Leu Thr Tyr Ala Ala Asp Leu				
	260		265	270
Val Glu Thr Met Lys Ser Gly Glu His Asp Phe Gly Ala Ala Phe Asp				
	275		280	285
Gly Asp Gly Asp Arg Asn Met Ile Leu Gly Lys His Gly Phe Phe Val				
	290		295	300
Asn Pro Ser Asp Ser Val Ala Val Ile Ala Ala Asn Ile Phe Ser Ile				
305		310		315 320
Pro Tyr Phe Gln Gln Thr Gly Val Arg Gly Phe Ala Arg Ser Met Pro				
	325		330	335
Thr Ser Gly Ala Leu Asp Arg Val Ala Ser Ala Thr Lys Ile Ala Leu				
	340		345	350
Tyr Glu Thr Pro Thr Gly Trp Lys Phe Phe Gly Asn Leu Met Asp Ala				
	355		360	365
Ser Lys Leu Ser Leu Cys Gly Glu Glu Ser Phe Gly Thr Gly Ser Asp				
	370		375	380
His Ile Arg Glu Lys Asp Gly Leu Trp Ala Val Leu Ala Trp Leu Ser				
385		390		395 400
Ile Leu Ala Thr Arg Lys Gln Ser Val Glu Asp Ile Leu Lys Asp His				
	405		410	415
Trp Gln Lys His Gly Arg Asn Phe Phe Thr Arg Tyr Asp Tyr Glu Glu				
	420		425	430
Val Glu Ala Glu Gly Ala Asn Lys Met Met Lys Asp Leu Glu Ala Leu				
	435		440	445

Met Phe Asp Arg Ser Phe Val Gly Lys Gln Phe Ser Ala Asn Asp Lys  
 450 455 460

Val Tyr Thr Val Glu Lys Ala Asp Asn Phe Glu Tyr Ser Asp Pro Val  
 465 470 475 480

Asp Gly Ser Ile Ser Arg Asn Gln Gly Leu Arg Leu Ile Phe Thr Asp  
 485 490 495

Gly Ser Arg Ile Val Phe Arg Leu Ser Gly Thr Gly Ser Ala Gly Ala  
 500 505 510

Thr Ile Arg Leu Tyr Ile Asp Ser Tyr Glu Lys Asp Val Ala Lys Ile  
 515 520 525

Asn Gln Asp Pro Gln Val Met Leu Ala Pro Leu Ile Ser Ile Ala Leu  
 530 535 540

Lys Val Ser Gln Leu Gln Glu Arg Thr Gly Arg Thr Ala Pro Thr Val  
 545 550 555 560

Ile Thr

<210> 190  
 <211> 204  
 <212> PRT  
 <213> Homo sapiens

<400> 190

Gly Glu Gly Glu Arg Pro Glu Glu Asp Ala Ala Ala Leu Glu Leu Ser  
 1 5 10 15

Ser Asp Glu Ala Val Glu Val Glu Glu Val Ile Glu Glu Ser Arg Ala  
 20 25 30

Glu Arg Ile Lys Arg Ser Gly Leu Arg Arg Val Asp Asp Phe Lys Lys  
 35 40 45

Ala Phe Ser Lys Glu Lys Met Glu Lys Thr Lys Val Arg Thr Arg Glu  
 50 55 60

Asn Leu Glu Lys Thr Arg Leu Lys Thr Lys Glu Asn Leu Glu Lys Thr  
65 70 75 80

Arg His Thr Leu Glu Lys Arg Met Asn Lys Leu Gly Thr Arg Leu Val  
85 90 95

Pro Ala Glu Arg Arg Glu Lys Leu Lys Thr Ser Arg Asp Lys Leu Arg  
100 105 110

Lys Ser Phe Thr Pro Asp His Val Val Tyr Ala Arg Ser Lys Thr Ala  
115 120 125

Val Tyr Lys Val Pro Pro Phe Thr Phe His Val Lys Lys Ile Arg Glu  
130 135 140

Gly Gln Val Glu Val Leu Lys Ala Thr Glu Met Val Glu Val Gly Ala  
145 150 155 160

Asp Asp Asp Glu Gly Gly Ala Glu Arg Gly Glu Ala Gly Asp Leu Arg  
165 170 175

Arg Gly Ser Ser Pro Asp Val His Ala Leu Leu Glu Ile Thr Glu Glu  
180 185 190

Ser Asp Ala Val Leu Val Asp Lys Ser Asp Ser Asp  
195 200

<210> 191  
<211> 345  
<212> PRT  
<213> Homo sapiens

<400> 191

Met Ser Leu Phe Gly Leu Leu Leu Leu Thr Ser Ala Leu Ala Gly Gln  
1 5 10 15

Arg Gln Gly Thr Gln Ala Glu Ser Asn Leu Ser Ser Lys Phe Gln Phe  
20 25 30

Ser Ser Asn Lys Glu Gln Asn Gly Val Gln Asp Pro Gln His Glu Arg  
35 40 45

Ile Ile Thr Val Ser Thr Asn Gly Ser Ile His Ser Pro Arg Phe Pro  
50 55 60

His Thr Tyr Pro Arg Asn Thr Val Leu Val Trp Arg Leu Val Ala Val  
 65 70 75 80

Glu Glu Asn Val Trp Ile Gln Leu Thr Phe Asp Glu Arg Phe Gly Leu  
 85 90 95

Glu Asp Pro Glu Asp Asp Ile Cys Lys Tyr Asp Phe Val Glu Val Glu  
 100 105 110

Glu Pro Ser Asp Gly Thr Ile Leu Gly Arg Trp Cys Gly Ser Gly Thr  
 115 120 125

Val Pro Gly Lys Gln Ile Ser Lys Gly Asn Gln Ile Arg Ile Arg Phe  
 130 135 140

Val Ser Asp Glu Tyr Phe Pro Ser Glu Pro Gly Phe Cys Ile His Tyr  
 145 150 155 160

Asn Ile Val Met Pro Gln Phe Thr Glu Ala Val Ser Pro Ser Val Leu  
 165 170 175

Pro Pro Ser Ala Leu Pro Leu Asp Leu Leu Asn Asn Ala Ile Thr Ala  
 180 185 190

Phe Ser Thr Leu Glu Asp Leu Ile Arg Tyr Leu Glu Pro Glu Arg Trp  
 195 200 205

Gln Leu Asp Leu Glu Asp Leu Tyr Arg Pro Thr Trp Gln Leu Leu Gly  
 210 215 220

Lys Ala Phe Val Phe Gly Arg Lys Ser Arg Val Val Asp Leu Asn Leu  
 225 230 235 240

Leu Thr Glu Glu Val Arg Leu Tyr Ser Cys Thr Pro Arg Asn Phe Ser  
 245 250 255

Val Ser Ile Arg Glu Glu Leu Lys Arg Thr Asp Thr Ile Phe Trp Pro  
 260 265 270

Gly Cys Leu Leu Val Lys Arg Cys Gly Gly Asn Cys Ala Cys Cys Leu  
 275 280 285

His Asn Cys Asn Glu Cys Gln Cys Val Pro Ser Lys Val Thr Lys Lys  
 290 295 300

Tyr His Glu Val Leu Gln Leu Arg Pro Lys Thr Gly Val Arg Gly Leu  
 305 310 315 320

His Lys Ser Leu Thr Asp Val Ala Leu Glu His His Glu Glu Cys Asp  
 325 330 335

Cys Val Cys Arg Gly Ser Thr Gly Gly  
 340 345

<210> 192  
 <211> 1261  
 <212> PRT  
 <213> Homo sapiens

<400> 192

Met Ile Ala His Lys Gln Lys Lys Thr Lys Lys Lys Arg Ala Trp Ala  
 1 5 10 15

Ser Gly Gln Leu Ser Thr Asp Ile Thr Thr Ser Glu Met Gly Leu Lys  
 20 25 30

Ser Leu Ser Ser Asn Ser Ile Phe Asp Pro Asp Tyr Ile Lys Glu Leu  
 35 40 45

Val Asn Asp Ile Arg Lys Phe Ser His Ile Leu Leu Tyr Leu Lys Glu  
 50 55 60

Ala Ile Phe Ser Asp Cys Phe Lys Glu Val Ile His Ile Arg Leu Glu  
 65 70 75 80

Glu Leu Leu Arg Val Leu Lys Ser Ile Met Asn Lys His Gln Asn Leu  
 85 90 95

Asn Ser Val Asp Leu Gln Asn Ala Ala Glu Met Leu Thr Ala Lys Val  
 100 105 110

Lys Ala Val Asn Phe Thr Glu Val Asn Glu Glu Asn Lys Asn Asp Leu  
 115 120 125

Phe Gln Glu Val Phe Ser Ser Ile Glu Thr Leu Ala Phe Thr Phe Gly

130

135

140

Asn Ile Leu Thr Asn Phe Leu Met Gly Asp Val Gly Asn Asp Ser Phe  
 145 150 155 160

Leu Arg Leu Pro Val Ser Arg Glu Thr Lys Ser Phe Glu Asn Val Ser  
 165 170 175

Val Glu Ser Val Asp Ser Ser Ser Glu Lys Gly Asn Phe Ser Pro Leu  
 180 185 190

Glu Leu Asp Asn Val Leu Leu Lys Asn Thr Asp Ser Ile Glu Leu Ala  
 195 200 205

Leu Ser Tyr Ala Lys Thr Trp Ser Lys Tyr Thr Lys Asn Ile Val Ser  
 210 215 220

Trp Val Glu Lys Lys Leu Asn Leu Glu Leu Glu Ser Thr Arg Asn Met  
 225 230 235 240

Val Lys Leu Ala Glu Ala Thr Arg Thr Asn Ile Gly Ile Gln Glu Phe  
 245 250 255

Met Pro Leu Gln Ser Leu Phe Thr Asn Ala Leu Leu Asn Asp Ile Glu  
 260 265 270

Ser Ser His Leu Leu Gln Gln Thr Ile Ala Ala Leu Gln Ala Asn Lys  
 275 280 285

Phe Val Gln Pro Leu Leu Gly Arg Lys Asn Glu Met Glu Lys Gln Arg  
 290 295 300

Lys Glu Ile Lys Glu Leu Trp Lys Gln Glu Gln Asn Lys Met Leu Glu  
 305 310 315 320

Ala Glu Asn Ala Leu Lys Lys Ala Lys Leu Leu Cys Met Gln Arg Gln  
 325 330 335

Asp Glu Tyr Glu Lys Ala Lys Ser Ser Met Phe Arg Ala Glu Glu Glu  
 340 345 350

His Leu Ser Ser Ser Gly Gly Leu Ala Lys Asn Leu Asn Lys Gln Leu  
 355 360 365

Glu Lys Lys Arg Arg Leu Glu Glu Glu Ala Leu Gln Lys Val Glu Glu  
 370 375 380

Ala Asp Glu Leu Tyr Lys Val Cys Val Thr Asn Val Glu Glu Arg Arg  
 385 390 395 400

Asn Asp Val Glu Asn Thr Lys Arg Glu Ile Leu Ala Gln Leu Arg Thr  
 405 410 415

Leu Val Phe Gln Cys Asp Leu Thr Leu Lys Ala Val Thr Val Asn Leu  
 420 425 430

Phe His Met Gln His Leu Gln Ala Ala Ser Leu Ala Asp Arg Leu Gln  
 435 440 445

Ser Leu Cys Gly Ser Ala Lys Leu Tyr Asp Pro Gly Gln Glu Tyr Ser  
 450 455 460

Glu Phe Val Lys Ala Thr Asn Ser Thr Glu Glu Glu Lys Val Asp Gly  
 465 470 475 480

Asn Val Asn Lys His Leu Asn Ser Ser Gln Pro Ser Gly Phe Gly Pro  
 485 490 495

Ala Asn Ser Leu Glu Asp Val Val Arg Leu Pro Asp Ser Ser Asn Lys  
 500 505 510

Ile Glu Glu Asp Arg Cys Ser Asn Ser Ala Asp Ile Thr Gly Pro Ser  
 515 520 525

Phe Ile Arg Ser Trp Thr Phe Gly Met Phe Ser Asp Ser Glu Ser Thr  
 530 535 540

Gly Gly Ser Ser Glu Ser Arg Ser Leu Asp Ser Glu Ser Ile Ser Pro  
 545 550 555 560

Gly Asp Phe His Arg Lys Leu Pro Arg Thr Pro Ser Ser Gly Thr Met  
 565 570 575

Ser Ser Ala Asp Asp Leu Asp Glu Arg Glu Pro Pro Ser Pro Ser Glu  
 580 585 590



Thr Gly Pro Asn Ser Leu Gly Thr Phe Lys Lys Thr Leu Met Ser Lys  
595 600 605

Ala Ala Leu Thr His Lys Phe Arg Lys Leu Arg Ser Pro Thr Lys Cys  
610 615 620

Arg Asp Cys Glu Gly Ile Val Val Phe Gln Gly Val Glu Cys Glu Glu  
625 630 635 640

Cys Leu Leu Val Cys His Arg Lys Cys Leu Glu Asn Leu Val Ile Ile  
645 650 655

Cys Gly His Gln Lys Leu Pro Gly Lys Ile His Leu Phe Gly Ala Glu  
660 665 670

Phe Thr Leu Val Ala Lys Lys Glu Pro Asp Gly Ile Pro Phe Ile Leu  
675 680 685

Lys Ile Cys Ala Ser Glu Ile Glu Asn Arg Ala Leu Cys Leu Gln Gly  
690 695 700

Ile Tyr Arg Val Cys Gly Asn Lys Ile Lys Thr Glu Lys Leu Cys Leu  
705 710 715 720

Ala Leu Glu Asn Gly Met His Leu Val Asp Ile Ser Glu Phe Ser Ser  
725 730 735

His Asp Ile Cys Asp Val Leu Lys Leu Tyr Leu Arg Gln Leu Pro Glu  
740 745 750

Pro Phe Ile Leu Phe Arg Leu Tyr Lys Glu Phe Ile Asp Leu Ala Lys  
755 760 765

Glu Ile Gln His Val Asn Glu Glu Gln Glu Thr Lys Lys Asn Ser Leu  
770 775 780

Glu Asp Lys Lys Trp Pro Asn Met Cys Ile Glu Ile Asn Arg Ile Leu  
785 790 795 800

Leu Lys Ser Lys Asp Leu Leu Arg Gln Leu Pro Ala Ser Asn Phe Asn  
805 810 815

Ser Leu His Phe Leu Ile Val His Leu Lys Arg Val Val Asp His Ala  
 820 825 830

Glu Glu Asn Lys Met Asn Ser Lys Asn Leu Gly Val Ile Phe Gly Pro  
 835 840 845

Ser Leu Ile Arg Pro Arg Pro Gln Thr Ala Pro Ile Thr Ile Ser Ser  
 850 855 860

Leu Ala Glu Tyr Ser Asn Gln Ala Arg Leu Val Glu Phe Leu Ile Thr  
 865 870 875 880

Tyr Ser Gln Lys Ile Phe Asp Gly Ser Leu Gln Pro Gln Asp Val Met  
 885 890 895

Cys Ser Ile Gly Val Val Asp Gln Gly Cys Phe Pro Lys Pro Leu Leu  
 900 905 910

Ser Pro Glu Glu Arg Asp Ile Glu Arg Ser Met Lys Ser Leu Phe Phe  
 915 920 925

Ser Ser Lys Glu Asp Ile His Thr Ser Glu Ser Glu Ser Lys Ile Phe  
 930 935 940

Glu Arg Ala Thr Ser Phe Glu Glu Ser Glu Arg Lys Gln Asn Ala Leu  
 945 950 955 960

Gly Lys Cys Asp Ala Cys Leu Ser Asp Lys Ala Gln Leu Leu Leu Asp  
 965 970 975

Gln Glu Ala Glu Ser Ala Ser Gln Lys Ile Glu Asp Gly Lys Ala Pro  
 980 985 990

Lys Pro Leu Ser Leu Lys Ser Asp Arg Ser Thr Asn Asn Val Glu Arg  
 995 1000 1005

His Thr Pro Arg Thr Lys Ile Arg Pro Val Ser Leu Pro Val Asp  
 1010 1015 1020

Arg Leu Leu Leu Ala Ser Pro Pro Asn Glu Arg Asn Gly Arg Asn  
 1025 1030 1035

Met Gly Asn Val Asn Leu Asp Lys Phe Cys Lys Asn Pro Ala Phe

1040		1045		1050
Glu Gly Val Asn Arg Lys Asp Ala Ala Thr Thr Val Cys Ser Lys				
1055		1060		1065
Phe Asn Gly Phe Asp Gln Gln Thr Leu Gln Lys Ile Gln Asp Lys				
1070		1075		1080
Gln Tyr Glu Gln Asn Ser Leu Thr Ala Lys Thr Thr Met Ile Met				
1085		1090		1095
Pro Ser Ala Leu Gln Glu Lys Gly Val Thr Thr Ser Leu Gln Ile				
1100		1105		1110
Ser Gly Asp His Ser Ile Asn Ala Thr Gln Pro Ser Lys Pro Tyr				
1115		1120		1125
Ala Glu Pro Val Arg Ser Val Arg Glu Ala Ser Glu Arg Arg Ser				
1130		1135		1140
Ser Asp Ser Tyr Pro Leu Ala Pro Val Arg Ala Pro Arg Thr Leu				
1145		1150		1155
Gln Pro Gln His Trp Thr Thr Phe Tyr Lys Pro His Ala Pro Ile				
1160		1165		1170
Ile Ser Ile Arg Gly Asn Glu Glu Lys Pro Ala Ser Pro Ser Ala				
1175		1180		1185
Ala Cys Pro Pro Gly Thr Asp His Asp Pro His Gly Leu Val Val				
1190		1195		1200
Lys Ser Met Pro Asp Pro Asp Lys Ala Ser Ala Cys Pro Gly Gln				
1205		1210		1215
Ala Thr Gly Gln Pro Lys Glu Asp Ser Glu Glu Leu Gly Leu Pro				
1220		1225		1230
Asp Val Asn Pro Met Cys Gln Arg Pro Arg Leu Lys Arg Met Gln				
1235		1240		1245
Gln Phe Glu Asp Leu Glu Asp Glu Ile Pro Gln Phe Val				
1250		1255		1260

<210> 193  
 <211> 192  
 <212> PRT  
 <213> Homo sapiens

<400> 193

Met Gln Ala Ile Lys Cys Val Val Val Gly Asp Gly Ala Val Gly Lys  
 1 5 10 15

Thr Cys Leu Leu Ile Ser Tyr Thr Thr Asn Ala Phe Pro Gly Glu Tyr  
 20 25 30

Ile Pro Thr Val Phe Asp Asn Tyr Ser Ala Asn Val Met Val Asp Ser  
 35 40 45

Lys Pro Val Asn Leu Gly Leu Trp Asp Thr Ala Gly Gln Glu Asp Tyr  
 50 55 60

Asp Arg Leu Arg Pro Leu Ser Tyr Pro Gln Thr Asp Val Phe Leu Ile  
 65 70 75 80

Cys Phe Ser Leu Val Ser Pro Ala Ser Tyr Glu Asn Val Arg Ala Lys  
 85 90 95

Trp Phe Pro Glu Val Arg His His Cys Pro Ser Thr Pro Ile Ile Leu  
 100 105 110

Val Gly Thr Lys Leu Asp Leu Arg Asp Asp Lys Asp Thr Ile Glu Lys  
 115 120 125

Leu Lys Glu Lys Lys Leu Ala Pro Ile Thr Tyr Pro Gln Gly Leu Ala  
 130 135 140

Leu Ala Lys Glu Ile Asp Ser Val Lys Tyr Leu Glu Cys Ser Ala Leu  
 145 150 155 160

Thr Gln Arg Gly Leu Lys Thr Val Phe Asp Glu Ala Ile Arg Ala Val  
 165 170 175

Leu Cys Pro Gln Pro Thr Arg Gln Gln Lys Arg Ala Cys Ser Leu Leu  
 180 185 190

<210> 194  
 <211> 404  
 <212> PRT  
 <213> Homo sapiens

<400> 194

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Met Asp Ser Arg Thr Lys Ser Lys Asp Tyr Cys Lys Val Ile Phe Pro
1           5           10           15

Tyr Glu Ala Gln Asn Asp Asp Glu Leu Thr Ile Lys Glu Gly Asp Ile
          20           25           30

Val Thr Leu Ile Asn Lys Asp Cys Ile Asp Val Gly Trp Trp Glu Gly
          35           40           45

Glu Leu Asn Gly Arg Arg Gly Val Phe Pro Asp Asn Phe Val Lys Leu
          50           55           60

Leu Pro Pro Asp Phe Glu Lys Glu Gly Asn Arg Pro Lys Lys Pro Pro
65           70           75           80

Pro Pro Ser Ala Pro Val Ile Lys Gln Gly Ala Gly Thr Thr Glu Arg
          85           90           95

Lys His Glu Ile Lys Lys Ile Pro Pro Glu Arg Pro Glu Met Leu Pro
          100          105          110

Asn Arg Thr Glu Glu Lys Glu Arg Pro Glu Arg Glu Pro Lys Leu Asp
          115          120          125

Leu Gln Lys Pro Ser Val Pro Ala Ile Pro Pro Lys Lys Pro Arg Pro
          130          135          140

Pro Lys Thr Asn Ser Leu Ser Arg Pro Gly Ala Leu Pro Pro Arg Arg
          145          150          155          160

Pro Glu Arg Pro Val Gly Pro Leu Thr His Thr Arg Gly Asp Ser Pro
          165          170          175

Lys Ile Asp Leu Ala Gly Ser Ser Leu Ser Gly Ile Leu Asp Lys Asp
          180          185          190

Leu Ser Asp Arg Ser Asn Asp Ile Asp Leu Glu Gly Phe Asp Ser Val
          195          200          205

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Val Ser Ser Thr Glu Lys Leu Ser His Pro Thr Thr Ser Arg Pro Lys  
 210 215 220

Ala Thr Gly Arg Arg Pro Pro Ser Gln Ser Leu Thr Ser Ser Ser Leu  
 225 230 235 240

Ser Ser Pro Asp Ile Phe Asp Ser Pro Ser Pro Glu Glu Asp Lys Glu  
 245 250 255

Glu His Ile Ser Leu Ala His Arg Gly Val Asp Ala Ser Lys Lys Thr  
 260 265 270

Ser Lys Thr Val Thr Ile Ser Gln Val Ser Asp Asn Lys Ala Ser Leu  
 275 280 285

Pro Pro Lys Pro Gly Thr Met Ala Ala Gly Gly Gly Gly Pro Ala Pro  
 290 295 300

Leu Ser Ser Ala Ala Pro Ser Pro Leu Ser Ser Ser Leu Gly Thr Ala  
 305 310 315 320

Gly His Arg Ala Asn Ser Pro Ser Leu Phe Gly Thr Glu Gly Lys Pro  
 325 330 335

Lys Met Glu Pro Ala Ala Ser Ser Gln Ala Ala Val Glu Glu Leu Arg  
 340 345 350

Thr Gln Val Arg Glu Leu Arg Ser Ile Ile Glu Thr Met Lys Asp Gln  
 355 360 365

Gln Lys Arg Glu Ile Lys Gln Leu Leu Ser Glu Leu Asp Glu Glu Lys  
 370 375 380

Lys Ile Arg Leu Arg Leu Gln Met Glu Val Asn Asp Ile Lys Lys Ala  
 385 390 395 400

Leu Gln Ser Lys

<210> 195  
 <211> 268  
 <212> PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 195

Met Pro Arg Ser Phe Leu Val Lys Lys His Phe Asn Ala Ser Lys Lys  
 1 5 10 15

Pro Asn Tyr Ser Glu Leu Asp Thr His Thr Val Ile Ile Ser Pro Tyr  
 20 25 30

Leu Tyr Glu Ser Tyr Ser Met Pro Val Ile Pro Gln Pro Glu Ile Leu  
 35 40 45

Ser Ser Gly Ala Tyr Ser Pro Ile Thr Val Trp Thr Thr Ala Ala Pro  
 50 55 60

Phe His Ala Gln Leu Pro Asn Gly Leu Ser Pro Leu Ser Gly Tyr Ser  
 65 70 75 80

Ser Ser Leu Gly Arg Val Ser Pro Pro Pro Pro Ser Asp Thr Ser Ser  
 85 90 95

Lys Asp His Ser Gly Ser Glu Ser Pro Ile Ser Asp Glu Glu Glu Arg  
 100 105 110

Leu Gln Ser Lys Leu Ser Asp Pro His Ala Ile Glu Ala Glu Lys Phe  
 115 120 125

Gln Cys Asn Leu Cys Asn Lys Thr Tyr Ser Thr Phe Ser Gly Leu Ala  
 130 135 140

Lys His Lys Gln Leu His Cys Asp Ala Gln Ser Arg Lys Ser Phe Ser  
 145 150 155 160

Cys Lys Tyr Cys Asp Lys Glu Tyr Val Ser Leu Gly Ala Leu Lys Met  
 165 170 175

His Ile Arg Thr His Thr Leu Pro Cys Val Cys Lys Ile Cys Gly Lys  
 180 185 190

Ala Phe Ser Arg Pro Trp Leu Leu Gln Gly His Ile Arg Thr His Thr  
 195 200 205

Gly Glu Lys Pro Phe Ser Cys Pro His Cys Asn Arg Ala Phe Ala Asp

210

215

220

Arg Ser Asn Leu Arg Ala His Leu Gln Thr His Ser Asp Val Lys Lys  
 225 230 235 240

Tyr Gln Cys Lys Asn Cys Ser Lys Thr Phe Ser Arg Met Ser Leu Leu  
 245 250 255

His Lys His Glu Glu Ser Gly Cys Cys Val Ala His  
 260 265

<210> 196  
 <211> 490  
 <212> PRT  
 <213> Homo sapiens  
 <400> 196

Met Ser Glu Val Thr Lys Asn Ser Leu Glu Lys Ile Leu Pro Gln Leu  
 1 5 10 15

Lys Cys His Phe Thr Trp Asn Leu Phe Lys Glu Asp Ser Val Ser Arg  
 20 25 30

Asp Leu Glu Asp Arg Val Cys Asn Gln Ile Glu Phe Leu Asn Thr Glu  
 35 40 45

Phe Lys Ala Thr Met Tyr Asn Leu Leu Ala Tyr Ile Lys His Leu Asp  
 50 55 60

Gly Asn Asn Glu Ala Ala Leu Glu Cys Leu Arg Gln Ala Glu Glu Leu  
 65 70 75 80

Ile Gln Gln Glu His Ala Asp Gln Ala Glu Ile Arg Ser Leu Val Thr  
 85 90 95

Trp Gly Asn Tyr Ala Trp Val Tyr Tyr His Leu Gly Arg Leu Ser Asp  
 100 105 110

Ala Gln Ile Tyr Val Asp Lys Val Lys Gln Thr Cys Lys Lys Phe Ser  
 115 120 125

Asn Pro Tyr Ser Ile Glu Tyr Ser Glu Leu Asp Cys Glu Glu Gly Trp  
 130 135 140



Thr Gln Leu Lys Cys Gly Arg Asn Glu Arg Ala Lys Val Cys Phe Glu  
 145 150 155 160

Lys Ala Leu Glu Glu Lys Pro Asn Asn Pro Glu Phe Ser Ser Gly Leu  
 165 170 175

Ala Ile Ala Met Tyr His Leu Asp Asn His Pro Glu Lys Gln Phe Ser  
 180 185 190

Thr Asp Val Leu Lys Gln Ala Ile Glu Leu Ser Pro Asp Asn Gln Tyr  
 195 200 205

Val Lys Val Leu Leu Gly Leu Lys Leu Gln Lys Met Asn Lys Glu Ala  
 210 215 220

Glu Gly Glu Gln Phe Val Glu Glu Ala Leu Glu Lys Ser Pro Cys Gln  
 225 230 235 240

Thr Asp Val Leu Arg Ser Ala Ala Lys Phe Tyr Arg Arg Lys Gly Asp  
 245 250 255

Leu Asp Lys Ala Ile Glu Leu Phe Gln Arg Val Leu Glu Ser Thr Pro  
 260 265 270

Asn Asn Gly Tyr Leu Tyr His Gln Ile Gly Cys Cys Tyr Lys Ala Lys  
 275 280 285

Val Arg Gln Met Gln Asn Thr Gly Glu Ser Glu Ala Ser Gly Asn Lys  
 290 295 300

Glu Met Ile Glu Ala Leu Lys Gln Tyr Ala Met Asp Tyr Ser Asn Lys  
 305 310 315 320

Ala Leu Glu Lys Gly Leu Asn Pro Leu Asn Ala Tyr Ser Asp Leu Ala  
 325 330 335

Glu Phe Leu Glu Thr Glu Cys Tyr Gln Thr Pro Phe Asn Lys Glu Val  
 340 345 350

Pro Asp Ala Glu Lys Gln Gln Ser His Gln Arg Tyr Cys Asn Leu Gln  
 355 360 365

Lys Tyr Asn Gly Lys Ser Glu Asp Thr Ala Val Gln His Gly Leu Glu  
 370 375 380

Gly Leu Ser Ile Ser Lys Lys Ser Thr Asp Lys Glu Glu Ile Lys Asp  
 385 390 395 400

Gln Pro Gln Asn Val Ser Glu Asn Leu Leu Pro Gln Asn Ala Pro Asn  
 405 410 415

Tyr Trp Tyr Leu Gln Gly Leu Ile His Lys Gln Asn Gly Asp Leu Leu  
 420 425 430

Gln Ala Ala Lys Cys Tyr Glu Lys Glu Leu Gly Arg Leu Leu Arg Asp  
 435 440 445

Ala Pro Ser Gly Ile Gly Ser Ile Phe Leu Ser Ala Ser Glu Leu Glu  
 450 455 460

Asp Gly Ser Glu Glu Met Gly Gln Gly Ala Val Ser Ser Ser Pro Arg  
 465 470 475 480

Glu Leu Leu Ser Asn Ser Glu Gln Leu Asn  
 485 490

<210> 197  
 <211> 567  
 <212> PRT  
 <213> Homo sapiens

<400> 197

Met Gly Arg Gly Leu Leu Arg Gly Leu Trp Pro Leu His Ile Val Leu  
 1 5 10 15

Trp Thr Arg Ile Ala Ser Thr Ile Pro Pro His Val Gln Lys Ser Val  
 20 25 30

Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro  
 35 40 45

Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln  
 50 55 60

Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro  
 65 70 75 80

Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr  
 85 90 95

Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile  
 100 105 110

Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys  
 115 120 125

Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn  
 130 135 140

Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Leu  
 145 150 155 160

Leu Leu Val Ile Phe Gln Val Thr Gly Ile Ser Leu Leu Pro Pro Leu  
 165 170 175

Gly Val Ala Ile Ser Val Ile Ile Ile Phe Tyr Cys Tyr Arg Val Asn  
 180 185 190

Arg Gln Gln Lys Leu Ser Ser Thr Trp Glu Thr Gly Lys Thr Arg Lys  
 195 200 205

Leu Met Glu Phe Ser Glu His Cys Ala Ile Ile Leu Glu Asp Asp Arg  
 210 215 220

Ser Asp Ile Ser Ser Thr Cys Ala Asn Asn Ile Asn His Asn Thr Glu  
 225 230 235 240

Leu Leu Pro Ile Glu Leu Asp Thr Leu Val Gly Lys Gly Arg Phe Ala  
 245 250 255

Glu Val Tyr Lys Ala Lys Leu Lys Gln Asn Thr Ser Glu Gln Phe Glu  
 260 265 270

Thr Val Ala Val Lys Ile Phe Pro Tyr Glu Glu Tyr Ala Ser Trp Lys  
 275 280 285

Thr Glu Lys Asp Ile Phe Ser Asp Ile Asn Leu Lys His Glu Asn Ile  
 290 295 300

Leu Gln Phe Leu Thr Ala Glu Glu Arg Lys Thr Glu Leu Gly Lys Gln  
 305 310 315 320

Tyr Trp Leu Ile Thr Ala Phe His Ala Lys Gly Asn Leu Gln Glu Tyr  
 325 330 335

Leu Thr Arg His Val Ile Ser Trp Glu Asp Leu Arg Lys Leu Gly Ser  
 340 345 350

Ser Leu Ala Arg Gly Ile Ala His Leu His Ser Asp His Thr Pro Cys  
 355 360 365

Gly Arg Pro Lys Met Pro Ile Val His Arg Asp Leu Asn Ser Ser Asn  
 370 375 380

Ile Leu Val Lys Asn Asp Leu Thr Cys Cys Leu Cys Asp Phe Gly Leu  
 385 390 395 400

Ser Leu Arg Leu Asp Pro Thr Leu Ser Val Asp Asp Leu Ala Asn Ser  
 405 410 415

Gly Gln Val Gly Thr Ala Arg Tyr Met Ala Pro Glu Val Leu Glu Ser  
 420 425 430

Arg Met Asn Leu Glu Asn Ala Glu Ser Phe Lys Gln Thr Asp Val Tyr  
 435 440 445

Ser Met Ala Leu Val Leu Trp Glu Met Thr Ser Arg Cys Asn Ala Val  
 450 455 460

Gly Glu Val Lys Asp Tyr Glu Pro Pro Phe Gly Ser Lys Val Arg Glu  
 465 470 475 480

His Pro Cys Val Glu Ser Met Lys Asp Asn Val Leu Arg Asp Arg Gly  
 485 490 495

Arg Pro Glu Ile Pro Ser Phe Trp Leu Asn His Gln Gly Ile Gln Met  
 500 505 510

Val Cys Glu Thr Leu Thr Glu Cys Trp Asp His Asp Pro Glu Ala Arg  
 515 520 525

Leu Thr Ala Gln Cys Val Ala Glu Arg Phe Ser Glu Leu Glu His Leu  
 530 535 540

Asp Arg Leu Ser Gly Arg Ser Cys Ser Glu Glu Lys Ile Pro Glu Asp  
 545 550 555 560

Gly Ser Leu Asn Thr Thr Lys  
 565

<210> 198  
 <211> 425  
 <212> PRT  
 <213> Homo sapiens

<400> 198

Met Ser Ser Ile Leu Pro Phe Thr Pro Pro Ile Val Lys Arg Leu Leu  
 1 5 10 15

Gly Trp Lys Lys Gly Glu Gln Asn Gly Gln Glu Glu Lys Trp Cys Glu  
 20 25 30

Lys Ala Val Lys Ser Leu Val Lys Lys Leu Lys Lys Thr Gly Gln Leu  
 35 40 45

Asp Glu Leu Glu Lys Ala Ile Thr Thr Gln Asn Val Asn Thr Lys Cys  
 50 55 60

Ile Thr Ile Pro Arg Ser Leu Asp Gly Arg Leu Gln Val Ser His Arg  
 65 70 75 80

Lys Gly Leu Pro His Val Ile Tyr Cys Arg Leu Trp Arg Trp Pro Asp  
 85 90 95

Leu His Ser His His Glu Leu Arg Ala Met Glu Leu Cys Glu Phe Ala  
 100 105 110

Phe Asn Met Lys Lys Asp Glu Val Cys Val Asn Pro Tyr His Tyr Gln  
 115 120 125

Arg Val Glu Thr Pro Val Leu Pro Pro Val Leu Val Pro Arg His Thr  
 130 135 140

Glu Ile Pro Ala Glu Phe Pro Pro Leu Asp Asp Tyr Ser His Ser Ile  
 145 150 155 160

Pro Glu Asn Thr Asn Phe Pro Ala Gly Ile Glu Pro Gln Ser Asn Ile  
 165 170 175

Pro Glu Thr Pro Pro Pro Gly Tyr Leu Ser Glu Asp Gly Glu Thr Ser  
 180 185 190

Asp His Gln Met Asn His Ser Met Asp Ala Gly Ser Pro Asn Leu Ser  
 195 200 205

Pro Asn Pro Met Ser Pro Ala His Asn Asn Leu Asp Leu Gln Pro Val  
 210 215 220

Thr Tyr Cys Glu Pro Ala Phe Trp Cys Ser Ile Ser Tyr Tyr Glu Leu  
 225 230 235 240

Asn Gln Arg Val Gly Glu Thr Phe His Ala Ser Gln Pro Ser Met Thr  
 245 250 255

Val Asp Gly Phe Thr Asp Pro Ser Asn Ser Glu Arg Phe Cys Leu Gly  
 260 265 270

Leu Leu Ser Asn Val Asn Arg Asn Ala Ala Val Glu Leu Thr Arg Arg  
 275 280 285

His Ile Gly Arg Gly Val Arg Leu Tyr Tyr Ile Gly Gly Glu Val Phe  
 290 295 300

Ala Glu Cys Leu Ser Asp Ser Ala Ile Phe Val Gln Ser Pro Asn Cys  
 305 310 315 320

Asn Gln Arg Tyr Gly Trp His Pro Ala Thr Val Cys Lys Ile Pro Pro  
 325 330 335

Gly Cys Asn Leu Lys Ile Phe Asn Asn Gln Glu Phe Ala Ala Leu Leu  
 340 345 350

Ala Gln Ser Val Asn Gln Gly Phe Glu Ala Val Tyr Gln Leu Thr Arg  
 355 360 365

Met Cys Thr Ile Arg Met Ser Phe Val Lys Gly Trp Gly Ala Glu Tyr  
 370 375 380

Arg Arg Gln Thr Val Thr Ser Thr Pro Cys Trp Ile Glu Leu His Leu  
 385 390 395 400

Asn Gly Pro Leu Gln Trp Leu Asp Lys Val Leu Thr Gln Met Gly Ser  
 405 410 415

Pro Ser Ile Arg Cys Ser Ser Val Ser  
 420 425

<210> 199  
 <211> 655  
 <212> PRT  
 <213> Homo sapiens

<400> 199

Met Gly Thr Ser Pro Ser Ser Ser Thr Ala Leu Ala Ser Cys Ser Arg  
 1 5 10 15

Ile Ala Arg Arg Ala Thr Ala Thr Met Ile Ala Gly Ser Leu Leu Leu  
 20 25 30

Leu Gly Phe Leu Ser Thr Thr Thr Ala Gln Pro Glu Gln Lys Ala Ser  
 35 40 45

Asn Leu Ile Gly Thr Tyr Arg His Val Asp Arg Ala Thr Gly Gln Val  
 50 55 60

Leu Thr Cys Asp Lys Cys Pro Ala Gly Thr Tyr Val Ser Glu His Cys  
 65 70 75 80

Thr Asn Thr Ser Leu Arg Val Cys Ser Ser Cys Pro Val Gly Thr Phe  
 85 90 95

Thr Arg His Glu Asn Gly Ile Glu Lys Cys His Asp Cys Ser Gln Pro  
 100 105 110

Cys Pro Trp Pro Met Ile Glu Lys Leu Pro Cys Ala Ala Leu Thr Asp  
 115 120 125

Arg Glu Cys Thr Cys Pro Pro Gly Met Phe Gln Ser Asn Ala Thr Cys  
 130 135 140

Ala Pro His Thr Val Cys Pro Val Gly Trp Gly Val Arg Lys Lys Gly

334



Pro Ser Ala Ile Val Glu Lys Ala Gly Leu Lys Lys Ser Met Thr Pro  
 385 390 395 400

Thr Gln Asn Arg Glu Lys Trp Ile Tyr Tyr Cys Asn Gly His Gly Ile  
 405 410 415

Asp Ile Leu Lys Leu Val Ala Ala Gln Val Gly Ser Gln Trp Lys Asp  
 420 425 430

Ile Tyr Gln Phe Leu Cys Asn Ala Ser Glu Arg Glu Val Ala Ala Phe  
 435 440 445

Ser Asn Gly Tyr Thr Ala Asp His Glu Arg Ala Tyr Ala Ala Leu Gln  
 450 455 460

His Trp Thr Ile Arg Gly Pro Glu Ala Ser Leu Ala Gln Leu Ile Ser  
 465 470 475 480

Ala Leu Arg Gln His Arg Arg Asn Asp Val Val Glu Lys Ile Arg Gly  
 485 490 495

Leu Met Glu Asp Thr Thr Gln Leu Glu Thr Asp Lys Leu Ala Leu Pro  
 500 505 510

Met Ser Pro Ser Pro Leu Ser Pro Ser Pro Ile Pro Ser Pro Asn Ala  
 515 520 525

Lys Leu Glu Asn Ser Ala Leu Leu Thr Val Glu Pro Ser Pro Gln Asp  
 530 535 540

Lys Asn Lys Gly Phe Phe Val Asp Glu Ser Glu Pro Leu Leu Arg Cys  
 545 550 555 560

Asp Ser Thr Ser Ser Gly Ser Ser Ala Leu Ser Arg Asn Gly Ser Phe  
 565 570 575

Ile Thr Lys Glu Lys Lys Asp Thr Val Leu Arg Gln Val Arg Leu Asp  
 580 585 590

Pro Cys Asp Leu Gln Pro Ile Phe Asp Asp Met Leu His Phe Leu Asn  
 595 600 605

Pro Glu Glu Leu Arg Val Ile Glu Glu Ile Pro Gln Ala Glu Asp Lys  
 610 615 620

Leu Asp Arg Leu Phe Glu Ile Ile Gly Val Lys Ser Gln Glu Ala Ser  
 625 630 635 640

Gln Thr Leu Leu Asp Ser Val Tyr Ser His Leu Pro Asp Leu Leu  
 645 650 655

<210> 200  
 <211> 207  
 <212> PRT  
 <213> Homo sapiens

<400> 200

Met Ser Ser Asp Arg Gln Arg Ser Asp Asp Glu Ser Pro Ser Thr Ser  
 1 5 10 15

Ser Gly Ser Ser Asp Ala Asp Gln Arg Asp Pro Ala Ala Pro Glu Pro  
 20 25 30

Glu Glu Gln Glu Glu Arg Lys Pro Ser Ala Thr Gln Gln Lys Lys Asn  
 35 40 45

Thr Lys Leu Ser Ser Lys Thr Thr Ala Lys Leu Ser Thr Ser Ala Lys  
 50 55 60

Arg Ile Gln Lys Glu Leu Ala Glu Ile Thr Leu Asp Pro Pro Pro Asn  
 65 70 75 80

Cys Ser Ala Gly Pro Lys Gly Asp Asn Ile Tyr Glu Trp Arg Ser Thr  
 85 90 95

Ile Leu Gly Pro Pro Gly Ser Val Tyr Glu Gly Gly Val Phe Phe Leu  
 100 105 110

Asp Ile Thr Phe Ser Ser Asp Tyr Pro Phe Lys Pro Pro Lys Val Thr  
 115 120 125

Phe Arg Thr Arg Ile Tyr His Cys Asn Ile Asn Ser Gln Gly Val Ile  
 130 135 140

Cys Leu Asp Ile Leu Lys Asp Asn Trp Ser Pro Ala Leu Thr Ile Ser

145                                      150                                      155                                      160  
 Lys Val Leu Leu Ser Ile Cys Ser Leu Leu Thr Asp Cys Asn Pro Ala  
    165                                      170                                      175  
 Asp Pro Leu Val Gly Ser Ile Ala Thr Gln Tyr Leu Thr Asn Arg Ala  
    180                                      185                                      190  
 Glu His Asp Arg Ile Ala Arg Gln Trp Thr Lys Arg Tyr Ala Thr  
    195                                      200                                      205  
  
 <210> 201  
 <211> 572  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 201  
 Met Ala Ala Pro Arg Pro Ser Pro Ala Ile Ser Val Ser Val Ser Ala  
 1                                      5                                      10                                      15  
  
 Pro Ala Phe Tyr Ala Pro Gln Lys Lys Phe Gly Pro Val Val Ala Pro  
    20                                      25                                      30  
  
 Lys Pro Lys Val Asn Pro Phe Arg Pro Gly Asp Ser Glu Pro Pro Pro  
    35                                      40                                      45  
  
 Ala Pro Gly Ala Gln Arg Ala Gln Met Gly Arg Val Gly Glu Ile Pro  
    50                                      55                                      60  
  
 Pro Pro Pro Pro Glu Asp Phe Pro Leu Pro Pro Pro Pro Leu Ala Gly  
 65                                      70                                      75                                      80  
  
 Asp Gly Asp Asp Ala Glu Gly Ala Leu Gly Gly Ala Phe Pro Pro Pro  
    85                                      90                                      95  
  
 Pro Pro Pro Ile Glu Glu Ser Phe Pro Pro Ala Pro Leu Glu Glu Glu  
    100                                      105                                      110  
  
 Ile Phe Pro Ser Pro Pro Pro Pro Pro Glu Glu Glu Gly Gly Pro Glu  
    115                                      120                                      125  
  
 Ala Pro Ile Pro Pro Pro Pro Gln Pro Arg Glu Lys Val Ser Ser Ile  
    130                                      135                                      140

Asp Leu Glu Ile Asp Ser Leu Ser Ser Leu Leu Asp Asp Met Thr Lys  
 145 150 155 160

Asn Asp Pro Phe Lys Ala Arg Val Ser Ser Gly Tyr Val Pro Pro Pro  
 165 170 175

Val Ala Thr Pro Phe Ser Ser Lys Ser Ser Thr Lys Pro Ala Ala Gly  
 180 185 190

Gly Thr Ala Pro Leu Pro Pro Trp Lys Ser Pro Ser Ser Ser Gln Pro  
 195 200 205

Leu Pro Gln Val Pro Ala Pro Ala Gln Ser Gln Thr Gln Phe His Val  
 210 215 220

Gln Pro Gln Pro Gln Pro Lys Pro Gln Val Gln Leu His Val Gln Ser  
 225 230 235 240

Gln Thr Gln Pro Val Ser Leu Ala Asn Thr Gln Pro Arg Gly Pro Pro  
 245 250 255

Ala Ser Ser Pro Ala Pro Ala Pro Lys Phe Ser Pro Val Thr Pro Lys  
 260 265 270

Phe Thr Pro Val Ala Ser Lys Phe Ser Pro Gly Ala Pro Gly Gly Ser  
 275 280 285

Gly Ser Gln Pro Asn Gln Lys Leu Gly His Pro Glu Ala Leu Ser Ala  
 290 295 300

Gly Thr Gly Ser Pro Gln Pro Pro Ser Phe Thr Tyr Ala Gln Gln Arg  
 305 310 315 320

Glu Lys Pro Arg Val Gln Glu Lys Gln His Pro Val Pro Pro Pro Ala  
 325 330 335

Gln Asn Gln Asn Gln Val Arg Ser Pro Gly Ala Pro Gly Pro Leu Thr  
 340 345 350

Leu Lys Glu Val Glu Glu Leu Glu Gln Leu Thr Gln Gln Leu Met Gln  
 355 360 365

Asp Met Glu His Pro Gln Arg Gln Asn Val Ala Val Asn Glu Leu Cys  
 370 375 380

Gly Arg Cys His Gln Pro Leu Ala Arg Ala Gln Pro Ala Val Arg Ala  
 385 390 395 400

Leu Gly Gln Leu Phe His Ile Ala Cys Phe Thr Cys His Gln Cys Ala  
 405 410 415

Gln Gln Leu Gln Gly Gln Gln Phe Tyr Ser Leu Glu Gly Ala Pro Tyr  
 420 425 430

Cys Glu Gly Cys Tyr Thr Asp Thr Leu Glu Lys Cys Asn Thr Cys Gly  
 435 440 445

Glu Pro Ile Thr Asp Arg Met Leu Arg Ala Thr Gly Lys Ala Tyr His  
 450 455 460

Pro His Cys Phe Thr Cys Val Val Cys Ala Arg Pro Leu Glu Gly Thr  
 465 470 475 480

Ser Phe Ile Val Asp Gln Ala Asn Arg Pro His Cys Val Pro Asp Tyr  
 485 490 495

His Lys Gln Tyr Ala Pro Arg Cys Ser Val Cys Ser Glu Pro Ile Met  
 500 505 510

Pro Glu Pro Gly Arg Asp Glu Thr Val Arg Val Val Ala Leu Asp Lys  
 515 520 525

Asn Phe His Met Lys Cys Tyr Lys Cys Glu Asp Cys Gly Lys Pro Leu  
 530 535 540

Ser Ile Glu Ala Asp Asp Asn Gly Cys Phe Pro Leu Asp Gly His Val  
 545 550 555 560

Leu Cys Arg Lys Cys His Thr Ala Arg Ala Gln Thr  
 565 570

<210> 202  
 <211> 141  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 202

Met Thr Lys Gln His Glu Leu Gly Gly Leu Leu Ala Leu Val Gln Asn  
 1 5 10 15

Cys Gln Ser Glu Met Asn Ile Lys Asp Ser Arg Ala Val Gly Leu Ser  
 20 25 30

Val Lys Arg Leu Cys Ile Ser Phe Val Asp Glu Phe Cys Glu Arg Thr  
 35 40 45

Glu Arg Pro Leu Tyr Leu Ala Gln Gly Leu Phe Met Lys Arg Glu Thr  
 50 55 60

Tyr Trp Glu Val Gln Asp Ser Gly Ile Ser Pro Leu Leu Leu Leu Leu  
 65 70 75 80

Ser Thr Ala Leu Asp Cys Ser Pro Glu Ala Glu Thr Arg Gln Ser Pro  
 85 90 95

Gly Gly Arg Lys Met Leu Gln Glu Pro Thr Leu Ser Met Ser Leu Gln  
 100 105 110

Ile Leu Thr Gly Phe Leu Trp Val Gln Leu Trp Asn Trp Glu Thr Phe  
 115 120 125

Leu Arg Ile Arg Thr His Ser Thr Asp Ala Ser Cys Pro  
 130 135 140

<210> 203  
 <211> 430  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 203

Met Asp Glu Gln Pro Arg Leu Met His Ser His Ala Gly Val Gly Met  
 1 5 10 15

Ala Gly His Pro Gly Leu Ser Gln His Leu Gln Asp Gly Ala Gly Gly  
 20 25 30

Thr Glu Gly Glu Gly Gly Arg Lys Gln Asp Ile Gly Asp Ile Leu Gln  
 35 40 45

Gln Ile Met Thr Ile Thr Asp Gln Ser Leu Asp Glu Ala Gln Ala Arg  
 50 55 60

Lys His Ala Leu Asn Cys His Arg Met Lys Pro Ala Leu Phe Asn Val  
 65 70 75 80

Leu Cys Glu Ile Lys Glu Lys Thr Val Leu Ser Ile Arg Gly Ala Gln  
 85 90 95

Glu Glu Glu Pro Thr Asp Pro Gln Leu Met Arg Leu Asp Asn Met Leu  
 100 105 110

Leu Ala Glu Gly Val Ala Gly Pro Glu Lys Gly Gly Gly Ser Ala Ala  
 115 120 125

Ala Ala Ala Ala Ala Ala Ala Ser Gly Gly Ala Gly Ser Asp Asn Ser  
 130 135 140

Val Glu His Ser Asp Tyr Arg Ala Lys Leu Ser Gln Ile Arg Gln Ile  
 145 150 155 160

Tyr His Thr Glu Leu Glu Lys Tyr Glu Gln Ala Cys Asn Glu Phe Thr  
 165 170 175

Thr His Val Met Asn Leu Leu Arg Glu Gln Ser Arg Thr Arg Pro Ile  
 180 185 190

Ser Pro Lys Glu Ile Glu Arg Met Val Ser Ile Ile His Arg Lys Phe  
 195 200 205

Ser Ser Ile Gln Met Gln Leu Lys Gln Ser Thr Cys Glu Ala Val Met  
 210 215 220

Ile Leu Arg Ser Arg Phe Leu Asp Ala Arg Arg Lys Arg Arg Asn Phe  
 225 230 235 240

Asn Lys Gln Ala Thr Glu Ile Leu Asn Glu Tyr Phe Tyr Ser His Leu  
 245 250 255

Ser Asn Pro Tyr Pro Ser Glu Glu Ala Lys Glu Glu Leu Ala Lys Lys  
 260 265 270

Cys Gly Ile Thr Val Ser Gln Val Ser Asn Trp Phe Gly Asn Lys Arg

275

280

285

Ile Arg Tyr Lys Lys Asn Ile Gly Lys Phe Gln Glu Glu Ala Asn Ile  
 290 295 300

Tyr Ala Ala Lys Thr Ala Val Thr Ala Thr Asn Val Ser Ala His Gly  
 305 310 315 320

Ser Gln Ala Asn Ser Pro Ser Thr Pro Asn Ser Ala Gly Ser Ser Ser  
 325 330 335

Ser Phe Asn Met Ser Asn Ser Gly Asp Leu Phe Met Ser Val Gln Ser  
 340 345 350

Leu Asn Gly Asp Ser Tyr Gln Gly Ala Gln Val Gly Ala Asn Val Gln  
 355 360 365

Ser Gln Val Asp Thr Leu Arg His Val Ile Ser Gln Thr Gly Gly Tyr  
 370 375 380

Ser Asp Gly Leu Ala Ala Ser Gln Met Tyr Ser Pro Gln Gly Ile Ser  
 385 390 395 400

Ala Asn Gly Gly Trp Gln Asp Ala Thr Thr Pro Ser Ser Val Thr Ser  
 405 410 415

Pro Thr Glu Gly Pro Gly Ser Val His Ser Asp Thr Ser Asn  
 420 425 430

<210> 204  
 <211> 384  
 <212> PRT  
 <213> Homo sapiens

<400> 204

Ala Arg Gly Val Ala Ser Met Thr Met Asn Val Ile Gln Thr Val Pro  
 1 5 10 15

Asn Leu Asp Trp Leu Ser Val Trp Ile Lys Ala Tyr Ala Phe Val His  
 20 25 30

Thr Gly Asp Asn Ser Arg Ala Ile Ser Thr Ile Cys Ser Leu Glu Lys  
 35 40 45



Lys Ser Leu Leu Arg Asp Asn Val Asp Leu Leu Gly Ser Leu Ala Asp  
 50 55 60

Leu Tyr Phe Arg Ala Gly Asp Asn Lys Asn Ser Val Leu Lys Phe Glu  
 65 70 75 80

Gln Ala Gln Met Leu Asp Pro Tyr Leu Ile Lys Gly Met Asp Val Tyr  
 85 90 95

Gly Tyr Leu Leu Ala Arg Glu Gly Arg Leu Glu Asp Val Glu Asn Leu  
 100 105 110

Gly Cys Arg Leu Phe Asn Ile Ser Asp Gln His Ala Glu Pro Trp Val  
 115 120 125

Val Ser Gly Cys His Ser Phe Tyr Ser Lys Arg Tyr Ser Arg Ala Leu  
 130 135 140

Tyr Leu Gly Ala Lys Ala Ile Gln Leu Asn Ser Asn Ser Val Gln Ala  
 145 150 155 160

Leu Leu Leu Lys Gly Ala Ala Leu Arg Asn Met Gly Arg Val Gln Glu  
 165 170 175

Ala Ile Ile His Phe Arg Glu Ala Ile Arg Leu Ala Pro Cys Arg Leu  
 180 185 190

Asp Cys Tyr Glu Gly Leu Ile Glu Cys Tyr Leu Ala Ser Asn Ser Ile  
 195 200 205

Arg Glu Ala Met Val Met Ala Asn Asn Val Tyr Lys Thr Leu Gly Ala  
 210 215 220

Asn Ala Gln Thr Leu Thr Leu Leu Ala Thr Val Cys Leu Glu Asp Pro  
 225 230 235 240

Val Thr Gln Glu Lys Ala Lys Thr Leu Leu Asp Lys Ala Leu Thr Gln  
 245 250 255

Arg Pro Asp Tyr Ile Lys Ala Val Val Lys Lys Ala Glu Leu Leu Ser  
 260 265 270

Arg Glu Gln Lys Tyr Glu Asp Gly Ile Ala Leu Leu Arg Asn Ala Leu  
 275 280 285

Ala Asn Gln Ser Asp Cys Val Leu His Arg Ile Leu Gly Asp Phe Leu  
 290 295 300

Val Ala Val Asn Glu Tyr Gln Glu Ala Met Asp Gln Tyr Ser Ile Ala  
 305 310 315 320

Leu Ser Leu Asp Pro Asn Asp Gln Lys Ser Leu Glu Gly Met Gln Lys  
 325 330 335

Met Glu Lys Glu Glu Ser Pro Thr Asp Ala Thr Gln Glu Glu Asp Val  
 340 345 350

Asp Asp Met Glu Gly Ser Gly Glu Glu Gly Asp Leu Glu Gly Ser Asp  
 355 360 365

Ser Glu Ala Ala Gln Trp Ala Asp Gln Glu Gln Trp Phe Gly Met Gln  
 370 375 380

<210> 205  
 <211> 1659  
 <212> PRT  
 <213> Homo sapiens

<400> 205

Met Glu Ala Pro Ser Gly Ser Glu Pro Gly Gly Asp Gly Ala Gly Asp  
 1 5 10 15

Cys Ala His Pro Asp Pro Arg Ala Pro Gly Ala Ala Ala Pro Ser Ser  
 20 25 30

Gly Pro Gly Pro Cys Ala Ala Ala Arg Glu Ser Glu Arg Gln Leu Arg  
 35 40 45

Leu Arg Leu Cys Val Leu Asn Glu Ile Leu Gly Thr Glu Arg Asp Tyr  
 50 55 60

Val Gly Thr Leu Arg Phe Leu Gln Ser Ala Phe Leu His Arg Ile Arg  
 65 70 75 80

Gln Asn Val Ala Asp Ser Val Glu Lys Gly Leu Thr Glu Glu Asn Val  
 85 90 95

Lys Val Leu Phe Ser Asn Ile Glu Asp Ile Leu Glu Val His Lys Asp  
 100 105 110

Phe Leu Ala Ala Leu Glu Tyr Cys Leu His Pro Glu Pro Gln Ser Gln  
 115 120 125

His Glu Leu Gly Asn Val Phe Leu Lys Phe Lys Asp Lys Phe Cys Val  
 130 135 140

Tyr Glu Glu Tyr Cys Ser Asn His Glu Lys Ala Leu Arg Leu Leu Val  
 145 150 155 160

Glu Leu Asn Lys Ile Pro Thr Val Arg Ala Phe Leu Leu Ser Cys Met  
 165 170 175

Leu Leu Gly Gly Arg Lys Thr Thr Asp Ile Pro Leu Glu Gly Tyr Leu  
 180 185 190

Leu Ser Pro Ile Gln Arg Ile Cys Lys Tyr Pro Leu Leu Leu Lys Glu  
 195 200 205

Leu Ala Lys Arg Thr Pro Gly Lys His Pro Asp His Pro Ala Val Gln  
 210 215 220

Ser Ala Leu Gln Ala Met Lys Thr Val Cys Ser Asn Ile Asn Glu Thr  
 225 230 235 240

Lys Arg Gln Met Glu Lys Leu Glu Ala Leu Glu Gln Leu Gln Ser His  
 245 250 255

Ile Glu Gly Trp Glu Gly Ser Asn Leu Thr Asp Ile Cys Thr Gln Leu  
 260 265 270

Leu Leu Gln Gly Thr Leu Leu Lys Ile Ser Ala Gly Asn Ile Gln Glu  
 275 280 285

Arg Ala Phe Phe Leu Phe Asp Asn Leu Leu Val Tyr Cys Lys Arg Lys  
 290 295 300

Ser Arg Val Thr Gly Ser Lys Lys Ser Thr Lys Arg Thr Lys Ser Ile  
 305 310 315 320

Asn Gly Ser Leu Tyr Ile Phe Arg Gly Arg Ile Asn Thr Glu Val Met  
 325 330 335

Glu Val Glu Asn Val Glu Asp Gly Thr Ala Asp Tyr His Ser Asn Gly  
 340 345 350

Tyr Thr Val Thr Asn Gly Trp Lys Ile His Asn Thr Ala Lys Asn Lys  
 355 360 365

Trp Phe Val Cys Met Ala Lys Thr Ala Glu Glu Lys Gln Lys Trp Leu  
 370 375 380

Asp Ala Ile Ile Arg Glu Arg Glu Gln Arg Glu Ser Leu Lys Leu Gly  
 385 390 395 400

Met Glu Arg Asp Ala Tyr Val Met Ile Ala Glu Lys Gly Glu Lys Leu  
 405 410 415

Tyr His Met Met Met Asn Lys Lys Val Asn Leu Ile Lys Asp Arg Arg  
 420 425 430

Arg Lys Leu Ser Thr Val Pro Lys Cys Phe Leu Gly Asn Glu Phe Val  
 435 440 445

Ala Trp Leu Leu Glu Ile Gly Glu Ile Ser Lys Thr Glu Glu Gly Val  
 450 455 460

Asn Leu Gly Gln Ala Leu Leu Glu Asn Gly Ile Ile His His Val Ser  
 465 470 475 480

Asp Lys His Gln Phe Lys Asn Glu Gln Val Met Tyr Arg Phe Arg Tyr  
 485 490 495

Asp Asp Gly Thr Tyr Lys Ala Arg Ser Glu Leu Glu Asp Ile Met Ser  
 500 505 510

Lys Gly Val Arg Leu Tyr Cys Arg Leu His Ser Leu Tyr Thr Pro Val  
 515 520 525

Ile Lys Asp Arg Asp Tyr His Leu Lys Thr Tyr Lys Ser Val Leu Pro  
 530 535 540

Gly Ser Lys Leu Val Asp Trp Leu Leu Ala Gln Gly Asp Cys Gln Thr  
 545 550 555 560  
 Arg Glu Glu Ala Val Ala Leu Gly Val Gly Leu Cys Asn Asn Gly Phe  
 565 570 575  
 Met His His Val Leu Glu Lys Ser Glu Phe Arg Asp Glu Ser Gln Tyr  
 580 585 590  
 Phe Arg Phe His Ala Asp Glu Glu Met Glu Gly Thr Ser Ser Lys Asn  
 595 600 605  
 Lys Gln Leu Arg Asn Asp Phe Lys Leu Val Glu Asn Ile Leu Ala Lys  
 610 615 620  
 Arg Leu Leu Ile Leu Pro Gln Glu Glu Asp Tyr Gly Phe Asp Ile Glu  
 625 630 635 640  
 Glu Lys Asn Lys Ala Val Val Val Lys Ser Val Gln Arg Gly Ser Leu  
 645 650 655  
 Ala Glu Val Ala Gly Leu Gln Val Gly Arg Lys Ile Tyr Ser Ile Asn  
 660 665 670  
 Glu Asp Leu Val Phe Leu Arg Pro Phe Ser Glu Val Glu Ser Ile Leu  
 675 680 685  
 Asn Gln Ser Phe Cys Ser Arg Arg Pro Leu Arg Leu Leu Val Ala Thr  
 690 695 700  
 Lys Ala Lys Glu Ile Ile Lys Ile Pro Asp Gln Pro Asp Thr Leu Cys  
 705 710 715 720  
 Phe Gln Ile Arg Gly Ala Ala Pro Pro Tyr Val Tyr Ala Val Gly Arg  
 725 730 735  
 Gly Ser Glu Ala Met Ala Ala Gly Leu Cys Ala Gly Gln Cys Ile Leu  
 740 745 750  
 Lys Val Asn Gly Ser Asn Val Met Asn Asp Gly Ala Pro Glu Val Leu  
 755 760 765  
 Glu His Phe Gln Ala Phe Arg Ser Arg Arg Glu Glu Ala Leu Gly Leu

770

775

780

Tyr Gln Trp Ile Tyr His Thr His Glu Asp Ala Gln Glu Ala Arg Ala  
 785 790 795 800

Ser Gln Glu Ala Ser Thr Glu Asp Pro Ser Gly Glu Gln Ala Gln Glu  
 805 810 815

Glu Asp Gln Ala Asp Ser Ala Phe Pro Leu Leu Ser Leu Gly Pro Arg  
 820 825 830

Leu Ser Leu Cys Glu Asp Ser Pro Met Val Thr Leu Thr Val Asp Asn  
 835 840 845

Val His Leu Glu His Gly Val Val Tyr Glu Tyr Val Ser Thr Ala Gly  
 850 855 860

Val Arg Cys His Val Leu Glu Lys Ile Val Glu Pro Arg Gly Cys Phe  
 865 870 875 880

Gly Leu Thr Ala Lys Ile Leu Glu Ala Phe Ala Ala Asn Asp Ser Val  
 885 890 895

Phe Val Glu Asn Cys Arg Arg Leu Met Ala Leu Ser Ser Ala Ile Val  
 900 905 910

Thr Met Pro His Phe Glu Phe Arg Asn Ile Cys Asp Thr Lys Leu Glu  
 915 920 925

Ser Ile Gly Gln Arg Ile Ala Cys Tyr Gln Glu Phe Ala Ala Gln Leu  
 930 935 940

Lys Ser Arg Val Ser Pro Pro Phe Lys Gln Ala Pro Leu Glu Pro His  
 945 950 955 960

Pro Leu Cys Gly Leu Asp Phe Cys Pro Thr Asn Cys His Ile Asn Leu  
 965 970 975

Met Glu Val Ser Tyr Pro Lys Thr Thr Pro Ser Val Gly Arg Ser Phe  
 980 985 990

Ser Ile Arg Phe Gly Arg Lys Pro Ser Leu Ile Gly Leu Asp Pro Glu  
 995 1000 1005

Gln Gly	His Leu Asn Pro Met	Ser Tyr Thr Gln His	Cys Ile Thr
1010	1015	1020	
Thr Met	Ala Ala Pro Ser Trp	Lys Cys Leu Pro Ala	Ala Glu Gly
1025	1030	1035	
Asp Pro	Gln Gly Gln Gly Leu	His Asp Gly Ser Phe	Gly Pro Ala
1040	1045	1050	
Ser Gly	Thr Leu Gly Gln Glu	Asp Arg Gly Leu Ser	Phe Leu Leu
1055	1060	1065	
Lys Gln	Glu Asp Arg Glu Ile	Gln Asp Ala Tyr Leu	Gln Leu Phe
1070	1075	1080	
Thr Lys	Leu Asp Val Ala Leu	Lys Glu Met Lys Gln	Tyr Val Thr
1085	1090	1095	
Gln Ile	Asn Arg Leu Leu Ser	Thr Ile Thr Glu Pro	Thr Ser Gly
1100	1105	1110	
Gly Ser	Cys Asp Ala Ser Leu	Ala Glu Glu Ala Ser	Ser Leu Pro
1115	1120	1125	
Leu Val	Ser Glu Glu Ser Glu	Met Asp Arg Ser Asp	His Gly Gly
1130	1135	1140	
Ile Lys	Lys Val Cys Phe Lys	Val Ala Glu Glu Asp	Gln Glu Asp
1145	1150	1155	
Ser Gly	His Asp Thr Met Ser	Tyr Arg Asp Ser Tyr	Ser Glu Cys
1160	1165	1170	
Asn Ser	Asn Arg Asp Ser Val	Leu Ser Tyr Thr Ser	Val Arg Ser
1175	1180	1185	
Asn Ser	Ser Tyr Leu Gly Ser	Asp Glu Met Gly Ser	Gly Asp Glu
1190	1195	1200	
Leu Pro	Cys Asp Met Arg Ile	Pro Ser Asp Lys Gln	Asp Lys Leu
1205	1210	1215	

His Gly Cys Leu Glu His Leu Phe Asn Gln Val Asp Ser Ile Asn  
 1220 1225 1230  
 Ala Leu Leu Lys Gly Pro Val Met Ser Arg Ala Phe Glu Glu Thr  
 1235 1240 1245  
 Lys His Phe Pro Met Asn His Ser Leu Gln Glu Phe Lys Gln Lys  
 1250 1255 1260  
 Glu Glu Cys Thr Ile Arg Gly Arg Ser Leu Ile Gln Ile Ser Ile  
 1265 1270 1275  
 Gln Glu Asp Pro Trp Asn Leu Pro Asn Ser Ile Lys Thr Leu Val  
 1280 1285 1290  
 Asp Asn Ile Gln Arg Tyr Val Glu Asp Gly Lys Asn Gln Leu Leu  
 1295 1300 1305  
 Leu Ala Leu Leu Lys Cys Thr Asp Thr Glu Leu Gln Leu Arg Arg  
 1310 1315 1320  
 Asp Ala Ile Phe Cys Gln Ala Leu Val Ala Ala Val Cys Thr Phe  
 1325 1330 1335  
 Ser Glu Gln Leu Leu Ala Ala Leu Gly Tyr Arg Tyr Asn Asn Asn  
 1340 1345 1350  
 Gly Glu Tyr Glu Glu Ser Ser Arg Asp Ala Ser Arg Lys Trp Leu  
 1355 1360 1365  
 Glu Gln Val Ala Ala Thr Gly Val Leu Leu His Cys Gln Ser Leu  
 1370 1375 1380  
 Leu Ser Pro Ala Thr Val Lys Glu Glu Arg Thr Met Leu Glu Asp  
 1385 1390 1395  
 Ile Trp Val Thr Leu Ser Glu Leu Asp Asn Val Thr Phe Ser Phe  
 1400 1405 1410  
 Lys Gln Leu Asp Glu Asn Tyr Val Ala Asn Thr Asn Val Phe Tyr  
 1415 1420 1425



His Ile Glu Gly Ser Arg Gln Ala Leu Lys Val Ile Phe Tyr Leu  
 1430 1435 1440  
 Asp Ser Tyr His Phe Ser Lys Leu Pro Ser Arg Leu Glu Gly Gly  
 1445 1450 1455  
 Ala Ser Leu Arg Leu His Thr Ala Leu Phe Thr Lys Val Leu Glu  
 1460 1465 1470  
 Asn Val Glu Gly Leu Pro Ser Pro Gly Ser Gln Ala Ala Glu Asp  
 1475 1480 1485  
 Leu Gln Gln Asp Ile Asn Ala Gln Ser Leu Glu Lys Val Gln Gln  
 1490 1495 1500  
 Tyr Tyr Arg Lys Leu Arg Ala Phe Tyr Leu Glu Arg Ser Asn Leu  
 1505 1510 1515  
 Pro Thr Asp Ala Ser Thr Thr Ala Val Lys Ile Asp Gln Leu Ile  
 1520 1525 1530  
 Arg Pro Ile Asn Ala Leu Asp Glu Leu Cys Arg Leu Met Lys Ser  
 1535 1540 1545  
 Phe Val His Pro Lys Pro Gly Ala Ala Gly Ser Val Gly Ala Gly  
 1550 1555 1560  
 Leu Ile Pro Ile Ser Ser Glu Leu Cys Tyr Arg Leu Gly Ala Cys  
 1565 1570 1575  
 Gln Met Val Met Cys Gly Thr Gly Met Gln Arg Ser Thr Leu Ser  
 1580 1585 1590  
 Val Ser Leu Glu Gln Ala Ala Ile Leu Ala Arg Ser His Gly Leu  
 1595 1600 1605  
 Leu Pro Lys Cys Ile Met Gln Ala Thr Asp Ile Met Arg Lys Gln  
 1610 1615 1620  
 Gly Pro Arg Val Glu Ile Leu Ala Lys Asn Leu Arg Val Lys Asp  
 1625 1630 1635  
 Gln Met Pro Gln Gly Ala Pro Arg Leu Tyr Arg Leu Cys Gln Pro

1640

1645

1650

Pro Val Asp Gly Asp Leu  
1655

&lt;210&gt; 206

&lt;211&gt; 175

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 206

Met Glu Lys Ile Pro Val Ser Ala Phe Leu Leu Leu Val Ala Leu Ser  
1 5 10 15

Tyr Thr Leu Ala Arg Asp Thr Thr Val Lys Pro Gly Ala Lys Lys Asp  
20 25 30

Thr Lys Asp Ser Arg Pro Lys Leu Pro Gln Thr Leu Ser Arg Gly Trp  
35 40 45

Gly Asp Gln Leu Ile Trp Thr Gln Thr Tyr Glu Glu Ala Leu Tyr Lys  
50 55 60

Ser Lys Thr Ser Asn Lys Pro Leu Met Ile Ile His His Leu Asp Glu  
65 70 75 80

Cys Pro His Ser Gln Ala Leu Lys Lys Val Phe Ala Glu Asn Lys Glu  
85 90 95

Ile Gln Lys Leu Ala Glu Gln Phe Val Leu Leu Asn Leu Val Tyr Glu  
100 105 110

Thr Thr Asp Lys His Leu Ser Pro Asp Gly Gln Tyr Val Pro Arg Ile  
115 120 125

Met Phe Val Asp Pro Ser Leu Thr Val Arg Ala Asp Ile Thr Gly Arg  
130 135 140

Tyr Ser Asn Arg Leu Tyr Ala Tyr Glu Pro Ala Asp Thr Ala Leu Leu  
145 150 155 160

Leu Asp Asn Met Lys Lys Ala Leu Lys Leu Leu Lys Thr Glu Leu  
165 170 175

<210> 207  
 <211> 196  
 <212> PRT  
 <213> Homo sapiens

<400> 207

Met Ala Ala Ile Arg Lys Lys Leu Val Val Val Gly Asp Gly Ala Cys  
 1 5 10 15

Gly Lys Thr Cys Leu Leu Ile Val Phe Ser Lys Asp Glu Phe Pro Glu  
 20 25 30

Val Tyr Val Pro Thr Val Phe Glu Asn Tyr Val Ala Asp Ile Glu Val  
 35 40 45

Asp Gly Lys Gln Val Glu Leu Ala Leu Trp Asp Thr Ala Gly Gln Glu  
 50 55 60

Asp Tyr Asp Arg Leu Arg Pro Leu Ser Tyr Pro Asp Thr Asp Val Ile  
 65 70 75 80

Leu Met Cys Phe Ser Val Asp Ser Pro Asp Ser Leu Glu Asn Ile Pro  
 85 90 95

Glu Lys Trp Val Pro Glu Val Lys His Phe Cys Pro Asn Val Pro Ile  
 100 105 110

Ile Leu Val Ala Asn Lys Lys Asp Leu Arg Ser Asp Glu His Val Arg  
 115 120 125

Thr Glu Leu Ala Arg Met Lys Gln Glu Pro Val Arg Thr Asp Asp Gly  
 130 135 140

Arg Ala Met Ala Val Arg Ile Gln Ala Tyr Asp Tyr Leu Glu Cys Ser  
 145 150 155 160

Ala Lys Thr Lys Glu Gly Val Arg Glu Val Phe Glu Thr Ala Thr Arg  
 165 170 175

Ala Ala Leu Gln Lys Arg Tyr Gly Ser Gln Asn Gly Cys Ile Asn Cys  
 180 185 190

Cys Lys Val Leu

195

<210> 208  
 <211> 291  
 <212> PRT  
 <213> Homo sapiens  
 <400> 208

Met	Glu	Lys	Leu	Ala	Ala	Ser	Thr	Glu	Pro	Gln	Gly	Pro	Arg	Pro	Val
1				5					10					15	
Leu	Gly	Arg	Glu	Ser	Val	Gln	Val	Pro	Asp	Asp	Gln	Asp	Phe	Arg	Ser
			20					25					30		
Phe	Arg	Ser	Glu	Cys	Glu	Ala	Glu	Val	Gly	Trp	Asn	Leu	Thr	Tyr	Ser
		35					40					45			
Arg	Ala	Gly	Val	Ser	Val	Trp	Val	Gln	Ala	Val	Glu	Met	Asp	Arg	Thr
	50					55					60				
Leu	His	Lys	Ile	Lys	Cys	Arg	Met	Glu	Cys	Cys	Asp	Val	Pro	Ala	Glu
65					70					75					80
Thr	Leu	Tyr	Asp	Val	Leu	His	Asp	Ile	Glu	Tyr	Arg	Lys	Lys	Trp	Asp
				85					90					95	
Ser	Asn	Val	Ile	Glu	Thr	Phe	Asp	Ile	Ala	Arg	Leu	Thr	Val	Asn	Ala
			100					105					110		
Asp	Val	Gly	Tyr	Tyr	Ser	Trp	Arg	Cys	Pro	Lys	Pro	Leu	Lys	Asn	Arg
		115					120					125			
Asp	Val	Ile	Thr	Leu	Arg	Ser	Trp	Leu	Pro	Met	Gly	Ala	Asp	Tyr	Ile
	130					135					140				
Ile	Met	Asn	Tyr	Ser	Val	Lys	His	Pro	Lys	Tyr	Pro	Pro	Arg	Lys	Asp
145					150					155				160	
Leu	Val	Arg	Ala	Val	Ser	Ile	Gln	Thr	Gly	Tyr	Leu	Ile	Gln	Ser	Thr
				165					170					175	
Gly	Pro	Lys	Ser	Cys	Val	Ile	Thr	Tyr	Leu	Ala	Gln	Val	Asp	Pro	Lys
			180					185					190		

Gly Ser Leu Pro Lys Trp Val Val Asn Lys Ser Ser Gln Phe Leu Ala  
 195 200 205

Pro Lys Ala Met Lys Lys Met Tyr Lys Ala Cys Leu Lys Tyr Pro Glu  
 210 215 220

Trp Lys Gln Lys His Leu Pro His Phe Lys Pro Trp Leu His Pro Glu  
 225 230 235 240

Gln Ser Pro Leu Pro Ser Leu Ala Leu Ser Glu Leu Ser Val Gln His  
 245 250 255

Ala Asp Ser Leu Glu Asn Ile Asp Glu Ser Ala Val Ala Glu Ser Arg  
 260 265 270

Glu Glu Arg Met Gly Gly Ala Gly Gly Glu Gly Ser Asp Asp Asp Thr  
 275 280 285

Ser Leu Thr  
 290

<210> 209  
 <211> 358  
 <212> PRT  
 <213> Homo sapiens

<400> 209

Met Ser Ala Asp Ala Ala Ala Gly Ala Pro Leu Pro Arg Leu Cys Cys  
 1 5 10 15

Leu Glu Lys Gly Pro Asn Gly Tyr Gly Phe His Leu His Gly Glu Lys  
 20 25 30

Gly Lys Leu Gly Gln Tyr Ile Arg Leu Val Glu Pro Gly Ser Pro Ala  
 35 40 45

Glu Lys Ala Gly Leu Leu Ala Gly Asp Arg Leu Val Glu Val Asn Gly  
 50 55 60

Glu Asn Val Glu Lys Glu Thr His Gln Gln Val Val Ser Arg Ile Arg  
 65 70 75 80

Ala Ala Leu Asn Ala Val Arg Leu Leu Val Val Asp Pro Glu Thr Asp

85	90	95
Glu Gln Leu Gln Lys Leu Gly Val	Gln Val Arg Glu Glu Leu Leu Arg	
100	105	110
Ala Gln Glu Ala Pro Gly Gln Ala Glu Pro Pro Ala Ala Ala Glu Val		
115	120	125
Gln Gly Ala Gly Asn Glu Asn Glu Pro Arg Glu Ala Asp Lys Ser His		
130	135	140
Pro Glu Gln Arg Glu Leu Arg Pro Arg Leu Cys Thr Met Lys Lys Gly		
145	150	155
Pro Ser Gly Tyr Gly Phe Asn Leu His Ser Asp Lys Ser Lys Pro Gly		
165	170	175
Gln Phe Ile Arg Ser Val Asp Pro Asp Ser Pro Ala Glu Ala Ser Gly		
180	185	190
Leu Arg Ala Gln Asp Arg Ile Val Glu Val Asn Gly Val Cys Met Glu		
195	200	205
Gly Lys Gln His Gly Asp Val Val Ser Ala Ile Arg Ala Gly Gly Asp		
210	215	220
Glu Thr Lys Leu Leu Val Val Asp Arg Glu Thr Asp Glu Phe Phe Lys		
225	230	235
Lys Cys Arg Val Ile Pro Ser Gln Glu His Leu Asn Gly Pro Leu Pro		
245	250	255
Val Pro Phe Thr Asn Gly Glu Ile Gln Lys Glu Asn Ser Arg Glu Ala		
260	265	270
Leu Ala Glu Ala Ala Leu Glu Ser Pro Arg Pro Ala Leu Val Arg Ser		
275	280	285
Ala Ser Ser Asp Thr Ser Glu Glu Leu Asn Ser Gln Asp Ser Pro Pro		
290	295	300
Lys Gln Asp Ser Thr Ala Pro Ser Ser Thr Ser Ser Ser Asp Pro Ile		
305	310	315
		320

Leu Asp Phe Asn Ile Ser Leu Ala Met Ala Lys Glu Arg Ala His Gln  
                   325                  330                  335

Lys Arg Ser Ser Lys Arg Ala Pro Gln Met Asp Trp Ser Lys Lys Asn  
                   340                  345                  350

Glu Leu Phe Ser Asn Leu  
                   355

<210> 210  
 <211> 345  
 <212> PRT  
 <213> Homo sapiens

<400> 210

Met Gln Leu Glu Ile Gln Val Ala Leu Asn Phe Ile Ile Ser Tyr Leu  
 1                  5                  10                  15

Tyr Asn Lys Leu Pro Arg Arg Arg Val Asn Ile Phe Gly Glu Glu Leu  
                   20                  25                  30

Glu Arg Leu Leu Lys Lys Lys Tyr Glu Gly His Trp Tyr Pro Glu Lys  
                   35                  40                  45

Pro Tyr Lys Gly Ser Gly Phe Arg Cys Ile His Ile Gly Glu Lys Val  
                   50                  55                  60

Asp Pro Val Ile Glu Gln Ala Ser Lys Glu Ser Gly Leu Asp Ile Asp  
 65                  70                  75                  80

Asp Val Arg Gly Asn Leu Pro Gln Asp Leu Ser Val Trp Ile Asp Pro  
                   85                  90                  95

Phe Glu Val Ser Tyr Gln Ile Gly Glu Lys Gly Pro Val Lys Val Leu  
                   100                  105                  110

Tyr Val Asp Asp Asn Asn Glu Asn Gly Cys Glu Leu Asp Lys Glu Ile  
                   115                  120                  125

Lys Asn Ser Phe Asn Pro Glu Ala Gln Val Phe Met Pro Ile Ser Asp  
                   130                  135                  140

Pro Ala Ser Ser Val Ser Ser Ser Pro Ser Pro Pro Phe Gly His Ser  
145 150 155 160

Ala Ala Val Ser Pro Thr Phe Met Pro Arg Ser Thr Gln Pro Leu Thr  
165 170 175

Phe Thr Thr Ala Thr Phe Ala Ala Thr Lys Phe Gly Ser Thr Lys Met  
180 185 190

Lys Asn Ser Gly Arg Ser Asn Lys Val Ala Arg Thr Ser Pro Ile Asn  
195 200 205

Leu Gly Leu Asn Val Asn Asp Leu Leu Lys Gln Lys Ala Ile Ser Ser  
210 215 220

Ser Met His Ser Leu Tyr Gly Leu Gly Leu Gly Ser Gln Gln Gln Pro  
225 230 235 240

Gln Gln Gln Gln Gln Pro Ala Gln Pro Pro Pro Pro Pro Pro Pro Pro  
245 250 255

Gln Gln Gln Gln Gln Gln Lys Thr Ser Ala Leu Ser Pro Asn Ala Lys  
260 265 270

Glu Phe Ile Phe Pro Asn Met Gln Gly Gln Gly Ser Ser Thr Asn Gly  
275 280 285

Met Phe Pro Gly Asp Ser Pro Leu Asn Leu Ser Pro Leu Gln Tyr Ser  
290 295 300

Asn Ala Phe Asp Val Phe Ala Ala Tyr Gly Gly Leu Asn Glu Lys Ser  
305 310 315 320

Phe Val Asp Gly Leu Asn Phe Ser Leu Asn Asn Met Gln Tyr Ser Asn  
325 330 335

Gln Gln Phe Gln Pro Val Met Ala Asn  
340 345

<210> 211  
<211> 84  
<212> PRT  
<213> Homo sapiens



&lt;400&gt; 211

Met Ala Thr Met Glu Asn Lys Val Ile Cys Ala Leu Val Leu Val Ser  
 1 5 10 15

Met Leu Ala Leu Gly Thr Leu Ala Glu Ala Gln Thr Glu Thr Cys Thr  
 20 25 30

Val Ala Pro Arg Glu Arg Gln Asn Cys Gly Phe Pro Gly Val Thr Pro  
 35 40 45

Ser Gln Cys Ala Asn Lys Gly Cys Cys Phe Asp Asp Thr Val Arg Gly  
 50 55 60

Val Pro Trp Cys Phe Tyr Pro Asn Thr Ile Asp Val Pro Pro Glu Glu  
 65 70 75 80

Glu Cys Glu Phe

&lt;210&gt; 212

&lt;211&gt; 522

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 212

Gly Phe Leu Pro Ala Thr Lys Asn Leu Leu Asn Glu Lys Asn His Gly  
 1 5 10 15

Val Leu His Thr Ser Val Val Leu Leu Thr Glu Met Cys Glu Arg Ser  
 20 25 30

Pro Asp Met Leu Ala His Phe Arg Glu Asn Glu Lys Leu Val Pro Gln  
 35 40 45

Leu Val Arg Ile Leu Lys Asn Leu Ile Met Ser Gly Tyr Ser Pro Gly  
 50 55 60

His Asp Val Ser Gly Ile Ser Asp Pro Phe Leu Gln Val Arg Ile Leu  
 65 70 75 80

Arg Leu Leu Arg Ile Leu Gly Arg Asn Asp Asp Asp Ser Ser Glu Ala  
 85 90 95

Met Asn Asp Ile Leu Ala Gln Val Ala Thr Asn Thr Glu Thr Ser Lys  
 100 105 110

Asn Val Gly Asn Ala Ile Leu Tyr Glu Thr Val Leu Thr Ile Met Asp  
 115 120 125

Ile Lys Ser Glu Ser Gly Leu Arg Val Leu Ala Ile Asn Ile Leu Gly  
 130 135 140

Arg Phe Leu Leu Asn Asn Asp Lys Asn Ile Arg Tyr Val Ala Leu Thr  
 145 150 155 160

Ser Leu Leu Lys Thr Val Gln Thr Asp His Asn Ala Val Gln Arg His  
 165 170 175

Arg Ser Thr Ile Val Asp Cys Leu Lys Asp Leu Asp Val Ser Ile Lys  
 180 185 190

Arg Arg Ala Met Glu Leu Ser Phe Ala Leu Val Asn Gly Asn Asn Ile  
 195 200 205

Arg Gly Met Met Lys Glu Leu Leu Tyr Phe Leu Asp Ser Cys Glu Pro  
 210 215 220

Glu Phe Lys Ala Asp Cys Ala Ser Gly Ile Phe Leu Ala Ala Glu Lys  
 225 230 235 240

Tyr Ala Pro Ser Lys Arg Trp His Ile Asp Thr Ile Met Arg Val Leu  
 245 250 255

Thr Thr Ala Gly Ser Tyr Val Arg Asp Asp Ala Val Pro Asn Leu Ile  
 260 265 270

Gln Leu Ile Thr Asn Ser Val Glu Met His Ala Tyr Thr Val Gln Arg  
 275 280 285

Leu Tyr Lys Ala Ile Leu Gly Asp Tyr Ser Gln Gln Pro Leu Val Gln  
 290 295 300

Val Ala Ala Trp Cys Ile Gly Glu Tyr Gly Asp Leu Leu Val Ser Gly  
 305 310 315 320

Gln Cys Glu Glu Glu Glu Pro Ile Gln Val Thr Glu Asp Glu Val Leu

361

Met Ala Val Leu Arg Gln Leu Ala Leu Leu Leu Trp Lys Asn Tyr Thr  
 1 5 10 15  
 Leu Gln Lys Arg Lys Val Leu Val Thr Val Leu Glu Leu Phe Leu Pro  
 20 25 30  
 Leu Leu Phe Pro Gly Ile Leu Ile Trp Leu Arg Leu Lys Ile Gln Ser  
 35 40 45  
 Glu Asn Val Pro Asn Ala Thr Ile Tyr Pro Gly Gln Ser Ile Gln Glu  
 50 55 60  
 Leu Pro Leu Phe Phe Thr Phe Pro Pro Pro Gly Asp Thr Trp Glu Leu  
 65 70 75 80  
 Ala Tyr Ile Pro Ser His Ser Asp Ala Ala Lys Thr Val Thr Glu Thr  
 85 90 95  
 Val Arg Arg Ala Leu Val Ile Asn Met Arg Val Arg Gly Phe Pro Ser  
 100 105 110  
 Glu Lys Asp Phe Glu Asp Tyr Ile Arg Tyr Asp Asn Cys Ser Ser Ser  
 115 120 125  
 Val Leu Ala Ala Val Val Phe Glu His Pro Phe Asn His Ser Lys Glu  
 130 135 140  
 Pro Leu Pro Leu Ala Val Lys Tyr His Leu Arg Phe Ser Tyr Thr Arg  
 145 150 155 160  
 Arg Asn Tyr Met Trp Thr Gln Thr Gly Ser Phe Phe Leu Lys Glu Thr  
 165 170 175  
 Glu Gly Trp His Thr Thr Ser Leu Phe Pro Leu Phe Pro Asn Pro Gly  
 180 185 190  
 Pro Arg Glu Leu Thr Ser Pro Asp Gly Gly Glu Pro Gly Tyr Ile Arg  
 195 200 205  
 Glu Gly Phe Leu Ala Val Gln His Ala Val Asp Arg Ala Ile Met Glu  
 210 215 220

Tyr His Ala Asp Ala Ala Thr Arg Gln Leu Phe Gln Arg Leu Thr Val  
 225 230 235 240  
 Thr Ile Lys Arg Phe Pro Tyr Pro Pro Phe Ile Ala Asp Pro Phe Leu  
 245 250 255  
 Val Ala Ile Gln Tyr Gln Leu Pro Leu Leu Leu Leu Ser Phe Thr  
 260 265 270  
 Tyr Thr Ala Leu Thr Ile Ala Arg Ala Val Val Gln Glu Lys Glu Arg  
 275 280 285  
 Arg Leu Lys Glu Tyr Met Arg Met Met Gly Leu Ser Ser Trp Leu His  
 290 295 300  
 Trp Ser Ala Trp Phe Leu Leu Phe Phe Leu Phe Leu Leu Ile Ala Ala  
 305 310 315 320  
 Ser Phe Met Thr Leu Leu Phe Cys Val Lys Val Lys Pro Asn Val Ala  
 325 330 335  
 Val Leu Ser Arg Ser Asp Pro Ser Leu Val Leu Ala Phe Leu Leu Cys  
 340 345 350  
 Phe Ala Ile Ser Thr Ile Ser Phe Ser Phe Met Val Ser Thr Phe Phe  
 355 360 365  
 Ser Lys Ala Asn Met Ala Ala Ala Phe Gly Gly Phe Leu Tyr Phe Phe  
 370 375 380  
 Thr Tyr Ile Pro Tyr Phe Phe Val Ala Pro Arg Tyr Asn Trp Met Thr  
 385 390 395 400  
 Leu Ser Gln Lys Leu Cys Ser Cys Leu Leu Ser Asn Val Ala Met Ala  
 405 410 415  
 Met Gly Ala Gln Leu Ile Gly Lys Phe Glu Ala Lys Gly Met Gly Ile  
 420 425 430  
 Gln Trp Arg Asp Leu Leu Ser Pro Val Asn Val Asp Asp Asp Phe Cys  
 435 440 445  
 Phe Gly Gln Val Leu Gly Met Leu Leu Leu Asp Ser Val Leu Tyr Gly

450                                      455                                      460  
 Leu Val Thr Trp Tyr Met Glu Ala Val Phe Pro Gly Gln Phe Gly Val  
 465                                      470                                      475                                      480  
 Pro Gln Pro Trp Tyr Phe Phe Ile Met Pro Ser Tyr Trp Cys Gly Lys  
 485                                      490                                      495  
 Pro Arg Ala Val Ala Gly Lys Glu Glu Glu Asp Ser Asp Pro Glu Lys  
 500                                      505                                      510  
 Ala Leu Arg Asn Glu Tyr Phe Glu Ala Glu Pro Glu Asp Leu Val Ala  
 515                                      520                                      525  
 Gly Ile Lys Ile Lys His Leu Ser Lys Val Phe Arg Val Gly Asn Lys  
 530                                      535                                      540  
 Asp Arg Ala Ala Val Arg Asp Leu Asn Leu Asn Leu Tyr Glu Gly Gln  
 545                                      550                                      555                                      560  
 Ile Thr Val Leu Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu  
 565                                      570                                      575  
 Ser Met Leu Thr Gly Leu Phe Pro Pro Thr Ser Gly Arg Ala Tyr Ile  
 580                                      585                                      590  
 Ser Gly Tyr Glu Ile Ser Gln Asp Met Val Gln Ile Arg Lys Ser Leu  
 595                                      600                                      605  
 Gly Leu Cys Pro Gln His Asp Ile Leu Phe Asp Asn Leu Thr Val Ala  
 610                                      615                                      620  
 Glu His Leu Tyr Phe Tyr Ala Gln Leu Lys Gly Leu Ser Arg Gln Lys  
 625                                      630                                      635                                      640  
 Cys Pro Glu Glu Val Lys Gln Met Leu His Ile Ile Gly Leu Glu Asp  
 645                                      650                                      655  
 Lys Trp Asn Ser Arg Ser Arg Phe Leu Ser Gly Gly Met Arg Arg Lys  
 660                                      665                                      670  
 Leu Ser Ile Gly Ile Ala Leu Ile Ala Gly Ser Lys Val Leu Ile Leu  
 675                                      680                                      685

Asp Glu Pro Thr Ser Gly Met Asp Ala Ile Ser Arg Arg Ala Ile Trp  
 690 695 700

Asp Leu Leu Gln Arg Gln Lys Ser Asp Arg Thr Ile Val Leu Thr Thr  
 705 710 715 720

His Phe Met Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Met  
 725 730 735

Ala Lys Gly Glu Leu Gln Cys Cys Gly Ser Ser Leu Phe Leu Lys Gln  
 740 745 750

Lys Tyr Gly Ala Gly Tyr His Met Thr Leu Val Lys Glu Pro His Cys  
 755 760 765

Asn Pro Glu Asp Ile Ser Gln Leu Val His His His Val Pro Asn Ala  
 770 775 780

Thr Leu Glu Ser Ser Ala Gly Ala Glu Leu Ser Phe Ile Leu Pro Arg  
 785 790 795 800

Glu Ser Thr His Arg Phe Glu Gly Leu Phe Ala Lys Leu Glu Lys Lys  
 805 810 815

Gln Lys Glu Leu Gly Ile Ala Ser Phe Gly Ala Ser Ile Thr Thr Met  
 820 825 830

Glu Glu Val Phe Leu Arg Val Gly Lys Leu Val Asp Ser Ser Met Asp  
 835 840 845

Ile Gln Ala Ile Gln Leu Pro Ala Leu Gln Tyr Gln His Glu Arg Arg  
 850 855 860

Ala Ser Asp Trp Ala Val Asp Ser Asn Leu Cys Gly Ala Met Asp Pro  
 865 870 875 880

Ser Asp Gly Ile Gly Ala Leu Ile Glu Glu Glu Arg Thr Ala Val Lys  
 885 890 895

Leu Asn Thr Gly Leu Ala Leu His Cys Gln Gln Phe Trp Ala Met Phe  
 900 905 910

Leu Lys Lys Ala Ala Tyr Ser Trp Arg Glu Trp Lys Met Val Ala Ala  
 915 920 925

Gln Val Leu Val Pro Leu Thr Cys Val Thr Leu Ala Leu Leu Ala Ile  
 930 935 940

Asn Tyr Ser Ser Glu Leu Phe Asp Asp Pro Met Leu Arg Leu Thr Leu  
 945 950 955 960

Gly Glu Tyr Gly Arg Thr Val Val Pro Phe Ser Val Pro Gly Thr Ser  
 965 970 975

Gln Leu Gly Gln Gln Leu Ser Glu His Leu Lys Asp Ala Leu Gln Ala  
 980 985 990

Glu Gly Gln Glu Pro Arg Glu Val Leu Gly Asp Leu Glu Glu Phe Leu  
 995 1000 1005

Ile Phe Arg Ala Ser Val Glu Gly Gly Gly Phe Asn Glu Arg Cys  
 1010 1015 1020

Leu Val Ala Ala Ser Phe Arg Asp Val Gly Glu Arg Thr Val Val  
 1025 1030 1035

Asn Ala Leu Phe Asn Asn Gln Ala Tyr His Ser Pro Ala Thr Ala  
 1040 1045 1050

Leu Ala Val Val Asp Asn Leu Leu Phe Lys Leu Leu Cys Gly Pro  
 1055 1060 1065

His Ala Ser Ile Val Val Ser Asn Phe Pro Gln Pro Arg Ser Ala  
 1070 1075 1080

Leu Gln Ala Ala Lys Asp Gln Phe Asn Glu Gly Arg Lys Gly Phe  
 1085 1090 1095

Asp Ile Ala Leu Asn Leu Leu Phe Ala Met Ala Phe Leu Ala Ser  
 1100 1105 1110

Thr Phe Ser Ile Leu Ala Val Ser Glu Arg Ala Val Gln Ala Lys  
 1115 1120 1125



His Val	Gln Phe Val Ser Gly	Val His Val Ala Ser	Phe Trp Leu
1130	1135	1140	
Ser Ala	Leu Leu Trp Asp Leu	Ile Ser Phe Leu Ile	Pro Ser Leu
1145	1150	1155	
Leu Leu	Leu Val Val Phe Lys	Ala Phe Asp Val Arg	Ala Phe Thr
1160	1165	1170	
Arg Asp	Gly His Met Ala Asp	Thr Leu Leu Leu Leu	Leu Leu Tyr
1175	1180	1185	
Gly Trp	Ala Ile Ile Pro Leu	Met Tyr Leu Met Asn	Phe Phe Phe
1190	1195	1200	
Leu Gly	Ala Ala Thr Ala Tyr	Thr Arg Leu Thr Ile	Phe Asn Ile
1205	1210	1215	
Leu Ser	Gly Ile Ala Thr Phe	Leu Met Val Thr Ile	Met Arg Ile
1220	1225	1230	
Pro Ala	Val Lys Leu Glu Glu	Leu Ser Lys Thr Leu	Asp His Val
1235	1240	1245	
Phe Leu	Val Leu Pro Asn His	Cys Leu Gly Met Ala	Val Ser Ser
1250	1255	1260	
Phe Tyr	Glu Asn Tyr Glu Thr	Arg Arg Tyr Cys Thr	Ser Ser Glu
1265	1270	1275	
Val Ala	Ala His Tyr Cys Lys	Lys Tyr Asn Ile Gln	Tyr Gln Glu
1280	1285	1290	
Asn Phe	Tyr Ala Trp Ser Ala	Pro Gly Val Gly Arg	Phe Val Ala
1295	1300	1305	
Ser Met	Ala Ala Ser Gly Cys	Ala Tyr Leu Ile Leu	Leu Phe Leu
1310	1315	1320	
Ile Glu	Thr Asn Leu Leu Gln	Arg Leu Arg Gly Ile	Leu Cys Ala
1325	1330	1335	
Leu Arg	Arg Arg Arg Thr Leu	Thr Glu Leu Tyr Thr	Arg Met Pro

1340		1345		1350
Val Leu Pro Glu Asp Gln Asp	Val Ala Asp Glu Arg Thr Arg Ile			
1355	1360	1365		
Leu Ala Pro Ser Pro Asp Ser	Leu Leu His Thr Pro Leu Ile Ile			
1370	1375	1380		
Lys Glu Leu Ser Lys Val Tyr	Glu Gln Arg Val Pro Leu Leu Ala			
1385	1390	1395		
Val Asp Arg Leu Ser Leu Ala	Val Gln Lys Gly Glu Cys Phe Gly			
1400	1405	1410		
Leu Leu Gly Phe Asn Gly Ala	Gly Lys Thr Thr Thr Phe Lys Met			
1415	1420	1425		
Leu Thr Gly Glu Glu Ser Leu	Thr Ser Gly Asp Ala Phe Val Gly			
1430	1435	1440		
Gly His Arg Ile Ser Ser Asp	Val Gly Lys Val Arg Gln Arg Ile			
1445	1450	1455		
Gly Tyr Cys Pro Gln Phe Asp	Ala Leu Leu Asp His Met Thr Gly			
1460	1465	1470		
Arg Glu Met Leu Val Met Tyr	Ala Arg Leu Arg Gly Ile Pro Glu			
1475	1480	1485		
Arg His Ile Gly Ala Cys Val	Glu Asn Thr Leu Arg Gly Leu Leu			
1490	1495	1500		
Leu Glu Pro His Ala Asn Lys	Leu Val Arg Thr Tyr Ser Gly Gly			
1505	1510	1515		
Asn Lys Arg Lys Leu Ser Thr	Gly Ile Ala Leu Ile Gly Glu Pro			
1520	1525	1530		
Ala Val Ile Phe Leu Asp Glu	Pro Ser Thr Gly Met Asp Pro Val			
1535	1540	1545		
Ala Arg Arg Leu Leu Trp Asp	Thr Val Ala Arg Ala Arg Glu Ser			
1550	1555	1560		

Gly Lys Ala Ile Ile Ile Thr Ser His Ser Met Glu Glu Cys Glu  
1565 1570 1575

Ala Leu Cys Thr Arg Leu Ala Ile Met Val Gln Gly Gln Phe Lys  
1580 1585 1590

Cys Leu Gly Ser Pro Gln His Leu Lys Ser Lys Phe Gly Ser Gly  
1595 1600 1605

Tyr Ser Leu Arg Ala Lys Val Gln Ser Glu Gly Gln Gln Glu Ala  
1610 1615 1620

Leu Glu Glu Phe Lys Ala Phe Val Asp Leu Thr Phe Pro Gly Ser  
1625 1630 1635

Val Leu Glu Asp Glu His Gln Gly Met Val His Tyr His Leu Pro  
1640 1645 1650

Gly Arg Asp Leu Ser Trp Ala Lys Val Phe Gly Ile Leu Glu Lys  
1655 1660 1665

Ala Lys Glu Lys Tyr Gly Val Asp Asp Tyr Ser Val Ser Gln Ile  
1670 1675 1680

Ser Leu Glu Gln Val Phe Leu Ser Phe Ala His Leu Gln Pro Pro  
1685 1690 1695

Thr Ala Glu Glu Gly Arg  
1700

<210> 214  
<211> 674  
<212> PRT  
<213> Homo sapiens

<400> 214

Met Ala Ala Phe Ser Val Gly Thr Ala Met Asn Ala Ser Ser Tyr Ser  
1 5 10 15

Ala Glu Met Thr Glu Pro Lys Ser Val Cys Val Ser Val Asp Glu Val  
20 25 30

Val Ser Ser Asn Met Glu Ala Thr Glu Thr Asp Leu Leu Asn Gly His  
           35                          40                          45

Leu Lys Lys Val Asp Asn Asn Leu Thr Glu Ala Gln Arg Phe Ser Ser  
       50                          55                          60

Leu Pro Arg Arg Ala Ala Val Asn Ile Glu Phe Arg Asp Leu Ser Tyr  
   65                          70                          75                          80

Ser Val Pro Glu Gly Pro Trp Trp Arg Lys Lys Gly Tyr Lys Thr Leu  
                           85                          90                          95

Leu Lys Gly Ile Ser Gly Lys Phe Asn Ser Gly Glu Leu Val Ala Ile  
                           100                          105                          110

Met Gly Pro Ser Gly Ala Gly Lys Ser Thr Leu Met Asn Ile Leu Ala  
       115                          120                          125

Gly Tyr Arg Glu Thr Gly Met Lys Gly Ala Val Leu Ile Asn Gly Leu  
       130                          135                          140

Pro Arg Asp Leu Arg Cys Phe Arg Lys Val Ser Cys Tyr Ile Met Gln  
   145                          150                          155                          160

Asp Asp Met Leu Leu Pro His Leu Thr Val Gln Glu Ala Met Met Val  
                           165                          170                          175

Ser Ala His Leu Lys Leu Gln Glu Lys Asp Glu Gly Arg Arg Glu Met  
                           180                          185                          190

Val Lys Glu Ile Leu Thr Ala Leu Gly Leu Leu Ser Cys Ala Asn Thr  
       195                          200                          205

Arg Thr Gly Ser Leu Ser Gly Gly Gln Arg Lys Arg Leu Ala Ile Ala  
   210                          215                          220

Leu Glu Leu Val Asn Asn Pro Pro Val Met Phe Phe Asp Glu Pro Thr  
   225                          230                          235                          240

Ser Gly Leu Asp Ser Ala Ser Cys Phe Gln Val Val Ser Leu Met Lys  
                           245                          250                          255

Gly Leu Ala Gln Gly Gly Arg Ser Ile Ile Cys Thr Ile His Gln Pro

260 265 270  
 Ser Ala Lys Leu Phe Glu Leu Phe Asp Gln Leu Tyr Val Leu Ser Gln  
 275 280 285  
 Gly Gln Cys Val Tyr Arg Gly Lys Val Cys Asn Leu Val Pro Tyr Leu  
 290 295 300  
 Arg Asp Leu Gly Leu Asn Cys Pro Thr Tyr His Asn Pro Ala Asp Phe  
 305 310 315 320  
 Val Met Glu Val Ala Ser Gly Glu Tyr Gly Asp Gln Asn Ser Arg Leu  
 325 330 335  
 Val Arg Ala Val Arg Glu Gly Met Cys Asp Ser Asp His Lys Arg Asp  
 340 345 350  
 Leu Gly Gly Asp Ala Glu Val Asn Pro Phe Leu Trp His Arg Pro Ser  
 355 360 365  
 Glu Glu Val Lys Gln Thr Lys Arg Leu Lys Gly Leu Arg Lys Asp Ser  
 370 375 380  
 Ser Ser Met Glu Gly Cys His Ser Phe Ser Ala Ser Cys Leu Thr Gln  
 385 390 395 400  
 Phe Cys Ile Leu Phe Lys Arg Thr Phe Leu Ser Ile Met Arg Asp Ser  
 405 410 415  
 Val Leu Thr His Leu Arg Ile Thr Ser His Ile Gly Ile Gly Leu Leu  
 420 425 430  
 Ile Gly Leu Leu Tyr Leu Gly Ile Gly Asn Glu Thr Lys Lys Val Leu  
 435 440 445  
 Ser Asn Ser Gly Phe Leu Phe Phe Ser Met Leu Phe Leu Met Phe Ala  
 450 455 460  
 Ala Leu Met Pro Thr Val Leu Thr Phe Pro Leu Glu Met Gly Val Phe  
 465 470 475 480  
 Leu Arg Glu His Leu Asn Tyr Trp Tyr Ser Leu Lys Ala Tyr Tyr Leu  
 485 490 495

Ala Lys Thr Met Ala Asp Val Pro Phe Gln Ile Met Phe Pro Val Ala  
                   500                                  505                                  510

Tyr Cys Ser Ile Val Tyr Trp Met Thr Ser Gln Pro Ser Asp Ala Val  
                   515                                  520                                  525

Arg Phe Val Leu Phe Ala Ala Leu Gly Thr Met Thr Ser Leu Val Ala  
                   530                                  535                                  540

Gln Ser Leu Gly Leu Leu Ile Gly Ala Ala Ser Thr Ser Leu Gln Val  
                   545                                  550                                  555                                  560

Ala Thr Phe Val Gly Pro Val Thr Ala Ile Pro Val Leu Leu Phe Ser  
                   565                                  570                                  575

Gly Phe Phe Val Ser Phe Asp Thr Ile Pro Thr Tyr Leu Gln Trp Met  
                   580                                  585                                  590

Ser Tyr Ile Ser Tyr Val Arg Tyr Gly Phe Glu Gly Val Ile Leu Ser  
                   595                                  600                                  605

Ile Tyr Gly Leu Asp Arg Glu Asp Leu His Cys Asp Ile Asp Glu Thr  
                   610                                  615                                  620

Cys His Phe Gln Lys Ser Glu Ala Ile Leu Arg Glu Leu Asp Val Glu  
                   625                                  630                                  635                                  640

Asn Ala Lys Leu Tyr Leu Asp Phe Ile Val Leu Gly Ile Phe Phe Ile  
                   645                                  650                                  655

Ser Leu Arg Leu Ile Ala Tyr Leu Val Leu Arg Tyr Lys Ile Arg Ala  
                   660                                  665                                  670

Glu Arg

<210> 215  
 <211> 149  
 <212> PRT  
 <213> Homo sapiens  
 <400> 215

Met Ala Asp Gln Leu Thr Glu Glu Gln Ile Ala Glu Phe Lys Glu Ala  
 1 5 10 15

Phe Ser Leu Phe Asp Lys Asp Gly Asp Gly Thr Ile Thr Thr Lys Glu  
 20 25 30

Leu Gly Thr Val Met Arg Ser Leu Gly Gln Asn Pro Thr Glu Ala Glu  
 35 40 45

Leu Gln Asp Met Ile Asn Glu Val Asp Ala Asp Gly Asn Gly Thr Ile  
 50 55 60

Asp Phe Pro Glu Phe Leu Thr Met Met Ala Arg Lys Met Lys Asp Thr  
 65 70 75 80

Asp Ser Glu Glu Glu Ile Arg Glu Ala Phe Arg Val Phe Asp Lys Asp  
 85 90 95

Gly Asn Gly Tyr Ile Ser Ala Ala Glu Leu Arg His Val Met Thr Asn  
 100 105 110

Leu Gly Glu Lys Leu Thr Asp Glu Glu Val Asp Glu Met Ile Arg Glu  
 115 120 125

Ala Asp Ile Asp Gly Asp Gly Gln Val Asn Tyr Glu Glu Phe Val Gln  
 130 135 140

Met Met Thr Ala Lys  
 145

<210> 216  
 <211> 354  
 <212> PRT  
 <213> Homo sapiens

<400> 216

Met Pro Arg Arg Ser Leu His Ala Ala Ala Val Leu Leu Leu Val Ile  
 1 5 10 15

Leu Lys Glu Gln Pro Ser Ser Pro Ala Pro Val Asn Gly Ser Lys Trp  
 20 25 30

Thr Tyr Phe Gly Pro Asp Gly Glu Asn Ser Trp Ser Lys Lys Tyr Pro  
 35 40 45

Ser Cys Gly Gly Leu Leu Gln Ser Pro Ile Asp Leu His Ser Asp Ile  
 50 55 60

Leu Gln Tyr Asp Ala Ser Leu Thr Pro Leu Glu Phe Gln Gly Tyr Asn  
 65 70 75 80

Leu Ser Ala Asn Lys Gln Phe Leu Leu Thr Asn Asn Gly His Ser Val  
 85 90 95

Lys Leu Asn Leu Pro Ser Asp Met His Ile Gln Gly Leu Gln Ser Arg  
 100 105 110

Tyr Ser Ala Thr Gln Leu His Leu His Trp Gly Asn Pro Asn Asp Pro  
 115 120 125

His Gly Ser Glu His Thr Val Ser Gly Gln His Phe Ala Ala Glu Leu  
 130 135 140

His Ile Val His Tyr Asn Ser Asp Leu Tyr Pro Asp Ala Ser Thr Ala  
 145 150 155 160

Ser Asn Lys Ser Glu Gly Leu Ala Val Leu Ala Val Leu Ile Glu Met  
 165 170 175

Gly Ser Phe Asn Pro Ser Tyr Asp Lys Ile Phe Ser His Leu Gln His  
 180 185 190

Val Lys Tyr Lys Gly Gln Glu Ala Phe Val Pro Gly Phe Asn Ile Glu  
 195 200 205

Glu Leu Leu Pro Glu Arg Thr Ala Glu Tyr Tyr Arg Tyr Arg Gly Ser  
 210 215 220

Leu Thr Thr Pro Pro Cys Asn Pro Thr Val Leu Trp Thr Val Phe Arg  
 225 230 235 240

Asn Pro Val Gln Ile Ser Gln Glu Gln Leu Leu Ala Leu Glu Thr Ala  
 245 250 255

Leu Tyr Cys Thr His Met Asp Asp Pro Ser Pro Arg Glu Met Ile Asn  
 260 265 270



Asn Phe Arg Gln Val Gln Lys Phe Asp Glu Arg Leu Val Tyr Thr Ser  
 275 280 285

Phe Ser Gln Val Gln Val Cys Thr Ala Ala Gly Leu Ser Leu Gly Ile  
 290 295 300

Ile Leu Ser Leu Ala Leu Ala Gly Ile Leu Gly Ile Cys Ile Val Val  
 305 310 315 320

Val Val Ser Ile Trp Leu Phe Arg Arg Lys Ser Ile Lys Lys Gly Asp  
 325 330 335

Asn Lys Gly Val Ile Tyr Lys Pro Ala Thr Lys Met Glu Thr Glu Ala  
 340 345 350

His Ala

<210> 217  
 <211> 244  
 <212> PRT  
 <213> Homo sapiens

<400> 217

Met Glu Leu Phe Leu Ala Gly Arg Arg Val Leu Val Thr Gly Ala Gly  
 1 5 10 15

Lys Gly Ile Gly Arg Gly Thr Val Gln Ala Leu His Ala Thr Gly Ala  
 20 25 30

Arg Val Val Ala Val Ser Arg Thr Gln Ala Asp Leu Asp Ser Leu Val  
 35 40 45

Arg Glu Cys Pro Gly Ile Glu Pro Val Cys Val Asp Leu Gly Asp Trp  
 50 55 60

Glu Ala Thr Glu Arg Ala Leu Gly Ser Val Gly Pro Val Asp Leu Leu  
 65 70 75 80

Val Asn Asn Ala Ala Val Ala Leu Leu Gln Pro Phe Leu Glu Val Thr  
 85 90 95

Lys Glu Ala Phe Asp Arg Ser Phe Glu Val Asn Leu Arg Ala Val Ile

100

105

110

Gln Val Ser Gln Ile Val Ala Arg Gly Leu Ile Ala Arg Gly Val Pro  
 115 120 125

Gly Ala Ile Val Asn Val Ser Ser Gln Cys Ser Gln Arg Ala Val Thr  
 130 135 140

Asn His Ser Val Tyr Cys Ser Thr Lys Gly Ala Leu Asp Met Leu Thr  
 145 150 155 160

Lys Val Met Ala Leu Glu Leu Gly Pro His Lys Ile Arg Val Asn Ala  
 165 170 175

Val Asn Pro Thr Val Val Met Thr Ser Met Gly Gln Ala Thr Trp Ser  
 180 185 190

Asp Pro His Lys Ala Lys Thr Met Leu Asn Arg Ile Pro Leu Gly Lys  
 195 200 205

Phe Ala Glu Val Glu His Val Val Asn Ala Ile Leu Phe Leu Leu Ser  
 210 215 220

Asp Arg Ser Gly Met Thr Thr Gly Ser Thr Leu Pro Val Glu Gly Gly  
 225 230 235 240

Phe Trp Ala Cys

<210> 218

<211> 756

<212> PRT

<213> Homo sapiens

<400> 218

Met Ala Glu Ala His Gln Ala Val Ala Phe Gln Phe Thr Val Thr Pro  
 1 5 10 15

Asp Gly Ile Asp Leu Arg Leu Ser His Glu Ala Leu Arg Gln Ile Tyr  
 20 25 30

Leu Ser Gly Leu His Ser Trp Lys Lys Lys Phe Ile Arg Phe Lys Asn  
 35 40 45

Gly Ile Ile Thr Gly Val Tyr Pro Ala Ser Pro Ser Ser Trp Leu Ile  
 50 55 60

Val Val Val Gly Val Met Thr Thr Met Tyr Ala Lys Ile Asp Pro Ser  
 65 70 75 80

Leu Gly Ile Ile Ala Lys Ile Asn Arg Thr Leu Glu Thr Ala Asn Cys  
 85 90 95

Met Ser Ser Gln Thr Lys Asn Val Val Ser Gly Val Leu Phe Gly Thr  
 100 105 110

Gly Leu Trp Val Ala Leu Ile Val Thr Met Arg Tyr Ser Leu Lys Val  
 115 120 125

Leu Leu Ser Tyr His Gly Trp Met Phe Thr Glu His Gly Lys Met Ser  
 130 135 140

Arg Ala Thr Lys Ile Trp Met Gly Met Val Lys Ile Phe Ser Gly Arg  
 145 150 155 160

Lys Pro Met Leu Tyr Ser Phe Gln Thr Ser Leu Pro Arg Leu Pro Val  
 165 170 175

Pro Ala Val Lys Asp Thr Val Asn Arg Tyr Leu Gln Ser Val Arg Pro  
 180 185 190

Leu Met Lys Glu Glu Asp Phe Lys Arg Met Thr Ala Leu Ala Gln Asp  
 195 200 205

Phe Ala Val Gly Leu Gly Pro Arg Leu Gln Trp Tyr Leu Lys Leu Lys  
 210 215 220

Ser Trp Trp Ala Thr Asn Tyr Val Ser Asp Trp Trp Glu Glu Tyr Ile  
 225 230 235 240

Tyr Leu Arg Gly Arg Gly Pro Leu Met Val Asn Ser Asn Tyr Tyr Ala  
 245 250 255

Met Asp Leu Leu Tyr Ile Leu Pro Thr His Ile Gln Ala Ala Arg Ala  
 260 265 270

Gly Asn Ala Ile His Ala Ile Leu Leu Tyr Arg Arg Lys Leu Asp Arg  
 275 280 285

Glu Glu Ile Lys Pro Ile Arg Leu Leu Gly Ser Thr Ile Pro Leu Cys  
 290 295 300

Ser Ala Gln Trp Glu Arg Met Phe Asn Thr Ser Arg Ile Pro Gly Glu  
 305 310 315 320

Glu Thr Asp Thr Ile Gln His Met Arg Asp Ser Lys His Ile Val Val  
 325 330 335

Tyr His Arg Gly Arg Tyr Phe Lys Val Trp Leu Tyr His Asp Gly Arg  
 340 345 350

Leu Leu Lys Pro Arg Glu Met Glu Gln Gln Met Gln Arg Ile Leu Asp  
 355 360 365

Asn Thr Ser Glu Pro Gln Pro Gly Glu Ala Arg Leu Ala Ala Leu Thr  
 370 375 380

Ala Gly Asp Arg Val Pro Trp Ala Arg Cys Arg Gln Ala Tyr Phe Gly  
 385 390 395 400

Arg Gly Lys Asn Lys Gln Ser Leu Asp Ala Val Glu Lys Ala Ala Phe  
 405 410 415

Phe Val Thr Leu Asp Glu Thr Glu Glu Gly Tyr Arg Ser Glu Asp Pro  
 420 425 430

Asp Thr Ser Met Asp Ser Tyr Ala Lys Ser Leu Leu His Gly Arg Cys  
 435 440 445

Tyr Asp Arg Trp Phe Asp Lys Ser Phe Thr Phe Val Val Phe Lys Asn  
 450 455 460

Gly Lys Met Gly Leu Asn Ala Glu His Ser Trp Ala Asp Ala Pro Ile  
 465 470 475 480

Val Ala His Leu Trp Glu Tyr Val Met Ser Ile Asp Ser Leu Gln Leu  
 485 490 495

Gly Tyr Ala Glu Asp Gly His Cys Lys Gly Asp Ile Asn Pro Asn Ile

500	505	510
Pro Tyr Pro Thr Arg Leu Gln Trp Asp Ile Pro Gly Glu Cys Gln Glu		
515	520	525
Val Ile Glu Thr Ser Leu Asn Thr Ala Asn Leu Leu Ala Asn Asp Val		
530	535	540
Asp Phe His Ser Phe Pro Phe Val Ala Phe Gly Lys Gly Ile Ile Lys		
545	550	555
Lys Cys Arg Thr Ser Pro Asp Ala Phe Val Gln Leu Ala Leu Gln Leu		
565	570	575
Ala His Tyr Lys Asp Met Gly Lys Phe Cys Leu Thr Tyr Glu Ala Ser		
580	585	590
Met Thr Arg Leu Phe Arg Glu Gly Arg Thr Glu Thr Val Arg Ser Cys		
595	600	605
Thr Thr Glu Ser Cys Asp Phe Val Arg Ala Met Val Asp Pro Ala Gln		
610	615	620
Thr Val Glu Gln Arg Leu Lys Leu Phe Lys Leu Ala Ser Glu Lys His		
625	630	635
Gln His Met Tyr Arg Leu Ala Met Thr Gly Ser Gly Ile Asp Arg His		
645	650	655
Leu Phe Cys Leu Tyr Val Val Ser Lys Tyr Leu Ala Val Glu Ser Pro		
660	665	670
Phe Leu Lys Glu Val Leu Ser Glu Pro Trp Arg Leu Ser Thr Ser Gln		
675	680	685
Thr Pro Gln Gln Gln Val Glu Leu Phe Asp Leu Glu Asn Asn Pro Glu		
690	695	700
Tyr Val Ser Ser Gly Gly Gly Phe Gly Pro Val Ala Asp Asp Gly Tyr		
705	710	715
Gly Val Ser Tyr Ile Leu Val Gly Glu Asn Leu Ile Asn Phe His Ile		
725	730	735

Ser Ser Lys Phe Ser Cys Pro Glu Thr Gly Ile Ile Ser Gln Gly Pro  
 740 745 750

Ser Ser Asp Thr  
 755

<210> 219  
 <211> 509  
 <212> PRT  
 <213> Homo sapiens

<400> 219

Met Gly Cys Ser Ala Lys Ala Arg Trp Ala Ala Gly Ala Leu Gly Val  
 1 5 10 15

Ala Gly Leu Leu Cys Ala Val Leu Gly Ala Val Met Ile Val Met Val  
 20 25 30

Pro Ser Leu Ile Lys Gln Gln Val Leu Lys Asn Val Arg Ile Asp Pro  
 35 40 45

Ser Ser Leu Ser Phe Asn Met Trp Lys Glu Ile Pro Ile Pro Phe Tyr  
 50 55 60

Leu Ser Val Tyr Phe Phe Asp Val Met Asn Pro Ser Glu Ile Leu Lys  
 65 70 75 80

Gly Glu Lys Pro Gln Val Arg Glu Arg Gly Pro Tyr Val Tyr Arg Glu  
 85 90 95

Ser Arg His Lys Ser Asn Ile Thr Phe Asn Asn Asn Asp Thr Val Ser  
 100 105 110

Phe Leu Glu Tyr Arg Thr Phe Gln Phe Gln Pro Ser Lys Ser His Gly  
 115 120 125

Ser Glu Ser Asp Tyr Ile Val Met Pro Asn Ile Leu Val Leu Gly Ala  
 130 135 140

Ala Val Met Met Glu Asn Lys Pro Met Thr Leu Lys Leu Ile Met Thr  
 145 150 155 160

Leu Ala Phe Thr Thr Leu Gly Glu Arg Ala Phe Met Asn Arg Thr Val  
 165 170 175

Gly Glu Ile Met Trp Gly Tyr Lys Asp Pro Leu Val Asn Leu Ile Asn  
 180 185 190

Lys Tyr Phe Pro Gly Met Phe Pro Phe Lys Asp Lys Phe Gly Leu Phe  
 195 200 205

Ala Glu Leu Asn Asn Ser Asp Ser Gly Leu Phe Thr Val Phe Thr Gly  
 210 215 220

Val Gln Asn Ile Ser Arg Ile His Leu Val Asp Lys Trp Asn Gly Leu  
 225 230 235 240

Ser Lys Val Asp Phe Trp His Ser Asp Gln Cys Asn Met Ile Asn Gly  
 245 250 255

Thr Ser Gly Gln Met Trp Pro Pro Phe Met Thr Pro Glu Ser Ser Leu  
 260 265 270

Glu Phe Tyr Ser Pro Glu Ala Cys Arg Ser Met Lys Leu Met Tyr Lys  
 275 280 285

Glu Ser Gly Val Phe Glu Gly Ile Pro Thr Tyr Arg Phe Val Ala Pro  
 290 295 300

Lys Thr Leu Phe Ala Asn Gly Ser Ile Tyr Pro Pro Asn Glu Gly Phe  
 305 310 315 320

Cys Pro Cys Leu Glu Ser Gly Ile Gln Asn Val Ser Thr Cys Arg Phe  
 325 330 335

Ser Ala Pro Leu Phe Leu Ser His Pro His Phe Leu Asn Ala Asp Pro  
 340 345 350

Val Leu Ala Glu Ala Val Thr Gly Leu His Pro Asn Gln Glu Ala His  
 355 360 365

Ser Leu Phe Leu Asp Ile His Pro Val Thr Gly Ile Pro Met Asn Cys  
 370 375 380

Ser Val Lys Leu Gln Leu Ser Leu Tyr Met Lys Ser Val Ala Gly Ile

382



Leu Gln Gly Ala Arg Ile Leu Gly Ile Pro Val Ile Val Thr Glu Gln  
85 90 95

Tyr Pro Lys Gly Leu Gly Ser Thr Val Gln Glu Ile Asp Leu Thr Gly  
100 105 110

Val Lys Leu Val Leu Pro Lys Thr Lys Phe Ser Met Val Leu Pro Glu  
115 120 125

Val Glu Ala Ala Leu Ala Glu Ile Pro Gly Val Arg Ser Val Val Leu  
130 135 140

Phe Gly Val Glu Thr His Val Cys Ile Gln Gln Thr Ala Leu Glu Leu  
145 150 155 160

Val Gly Arg Gly Val Glu Val His Ile Val Ala Asp Ala Thr Ser Ser  
165 170 175

Arg Ser Met Met Asp Arg Met Phe Ala Arg Leu Thr Ser Arg Ser Asn  
180 185 190

Gly Asp His Ser Asp His Glu  
195

<210> 221  
<211> 283  
<212> PRT  
<213> Homo sapiens

<400> 221

Met Thr Ser Gly Pro Gly Gly Pro Ala Ala Ala Ala Gly Gly Arg Lys  
1 5 10 15

Glu Asn His Gln Trp Tyr Val Cys Asn Arg Glu Lys Leu Cys Glu Ser  
20 25 30

Leu Gln Ala Val Phe Val Gln Ser Tyr Leu Asp Gln Gly Thr Gln Ile  
35 40 45

Phe Leu Asn Asn Ser Ile Glu Lys Ser Gly Trp Leu Phe Ile Gln Leu  
50 55 60

Tyr His Ser Phe Val Ser Ser Val Phe Ser Leu Phe Met Ser Arg Thr

65		70		75		80
Ser Ile Asn Gly	Leu Leu Gly Arg Gly	Ser Met Phe Val Phe	Ser Pro			
	85	90	95			
Asp Gln Phe Gln Arg Leu Leu Lys Ile Asn Pro Asp Trp Lys Thr His						
	100	105	110			
Arg Leu Leu Asp Leu Gly Ala Gly Asp Gly Glu Val Thr Lys Ile Met						
	115	120	125			
Ser Pro His Phe Glu Glu Ile Tyr Ala Thr Glu Leu Ser Glu Thr Met						
	130	135	140			
Ile Trp Gln Leu Gln Lys Lys Lys Tyr Arg Val Leu Gly Ile Asn Glu						
	145	150	155			160
Trp Gln Asn Thr Gly Phe Gln Tyr Asp Val Ile Ser Cys Leu Asn Leu						
	165	170	175			
Leu Asp Arg Cys Asp Gln Pro Leu Thr Leu Leu Lys Asp Ile Arg Ser						
	180	185	190			
Val Leu Glu Pro Thr Arg Gly Arg Val Ile Leu Ala Leu Val Leu Pro						
	195	200	205			
Phe His Pro Tyr Val Glu Asn Val Gly Gly Lys Trp Glu Lys Pro Ser						
	210	215	220			
Glu Ile Leu Glu Ile Lys Gly Gln Asn Trp Glu Glu Gln Val Asn Ser						
	225	230	235			240
Leu Pro Glu Val Phe Arg Lys Ala Gly Phe Val Ile Glu Ala Phe Thr						
	245	250	255			
Arg Leu Pro Tyr Leu Cys Glu Gly Asp Met Tyr Asn Asp Tyr Tyr Val						
	260	265	270			
Leu Asp Asp Ala Val Phe Val Leu Lys Pro Val						
	275	280				
<210>	222					
<211>	220					

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 222

Met Ser Met Gly Leu Glu Ile Thr Gly Thr Ala Leu Ala Val Leu Gly  
 1 5 10 15

Trp Leu Gly Thr Ile Val Cys Cys Ala Leu Pro Met Trp Arg Val Ser  
 20 25 30

Ala Phe Ile Gly Ser Asn Ile Ile Thr Ser Gln Asn Ile Trp Glu Gly  
 35 40 45

Leu Trp Met Asn Cys Val Val Gln Ser Thr Gly Gln Met Gln Cys Lys  
 50 55 60

Val Tyr Asp Ser Leu Leu Ala Leu Pro Gln Asp Leu Gln Ala Ala Arg  
 65 70 75 80

Ala Leu Ile Val Val Ala Ile Leu Leu Ala Ala Phe Gly Leu Leu Val  
 85 90 95

Ala Leu Val Gly Ala Gln Cys Thr Asn Cys Val Gln Asp Asp Thr Ala  
 100 105 110

Lys Ala Lys Ile Thr Ile Val Ala Gly Val Leu Phe Leu Leu Ala Ala  
 115 120 125

Leu Leu Thr Leu Val Pro Val Ser Trp Ser Ala Asn Thr Ile Ile Arg  
 130 135 140

Asp Phe Tyr Asn Pro Val Val Pro Glu Ala Gln Lys Arg Glu Met Gly  
 145 150 155 160

Ala Gly Leu Tyr Val Gly Trp Ala Ala Ala Ala Leu Gln Leu Leu Gly  
 165 170 175

Gly Ala Leu Leu Cys Cys Ser Cys Pro Pro Arg Glu Lys Lys Tyr Thr  
 180 185 190

Ala Thr Lys Val Val Tyr Ser Ala Pro Arg Ser Thr Gly Pro Gly Ala  
 195 200 205

Ser Leu Gly Thr Gly Tyr Asp Arg Lys Asp Tyr Val  
 210 215 220

<210> 223  
 <211> 251  
 <212> PRT  
 <213> Homo sapiens

<400> 223

Met Glu Gly Gly Ala Ala Ala Thr Pro Thr Ala Leu Pro Tyr Tyr  
 1 5 10 15

Val Ala Phe Ser Gln Leu Leu Gly Leu Thr Leu Val Ala Met Thr Gly  
 20 25 30

Ala Trp Leu Gly Leu Tyr Arg Gly Gly Ile Ala Trp Glu Ser Asp Leu  
 35 40 45

Gln Phe Asn Ala His Pro Leu Cys Met Val Ile Gly Leu Ile Phe Leu  
 50 55 60

Gln Gly Asn Ala Leu Leu Val Tyr Arg Val Phe Arg Asn Glu Ala Lys  
 65 70 75 80

Arg Thr Thr Lys Val Leu His Gly Leu Leu His Ile Phe Ala Leu Val  
 85 90 95

Ile Ala Leu Val Gly Leu Val Ala Val Phe Asp Tyr His Arg Lys Lys  
 100 105 110

Gly Tyr Ala Asp Leu Tyr Ser Leu His Ser Trp Cys Gly Ile Leu Val  
 115 120 125

Phe Val Leu Tyr Phe Val Gln Trp Leu Val Gly Phe Ser Phe Phe Leu  
 130 135 140

Phe Pro Gly Ala Ser Phe Ser Leu Arg Ser Arg Tyr Arg Pro Gln His  
 145 150 155 160

Ile Phe Phe Gly Ala Thr Ile Phe Leu Leu Pro Val Gly Thr Ala Leu  
 165 170 175

Leu Gly Leu Lys Glu Ala Leu Leu Phe Asn Leu Gly Gly Lys Tyr Ser  
 180 185 190

Ala Phe Glu Pro Glu Gly Val Leu Ala Asn Val Leu Gly Leu Leu Leu  
 195 200 205

Ala Cys Phe Gly Gly Ala Val Leu Tyr Ile Leu Thr Arg Ala Asp Trp  
 210 215 220

Lys Arg Pro Ser Gln Ala Glu Glu Gln Ala Leu Ser Met Asp Phe Lys  
 225 230 235 240

Thr Leu Arg Gln Gly Asp Ser Pro Gly Ser Gln  
 245 250

<210> 224  
 <211> 401  
 <212> PRT  
 <213> Homo sapiens

<400> 224

Tyr Val Cys Asn Cys Ser Val Val Gly Ser Leu Asn Val Asn Arg Cys  
 1 5 10 15

Asn Gln Thr Thr Gly Gln Cys Glu Cys Arg Pro Gly Tyr Gln Gly Leu  
 20 25 30

His Cys Glu Thr Cys Lys Glu Gly Phe Tyr Leu Asn Tyr Thr Ser Gly  
 35 40 45

Leu Cys Gln Pro Cys Asp Cys Ser Pro His Gly Ala Leu Ser Ile Pro  
 50 55 60

Cys Asn Ser Ser Gly Lys Cys Gln Cys Lys Val Gly Val Ile Gly Ser  
 65 70 75 80

Ile Cys Asp Arg Cys Gln Asp Gly Tyr Tyr Gly Phe Ser Lys Asn Gly  
 85 90 95

Cys Leu Pro Cys Gln Cys Asn Asn Arg Ser Ala Ser Cys Asp Ala Leu  
 100 105 110

Thr Gly Ala Cys Leu Asn Cys Gln Glu Asn Ser Lys Gly Asn His Cys  
 115 120 125

Glu Glu Cys Lys Glu Gly Phe Tyr Gln Ser Pro Asp Ala Thr Lys Glu  
 130 135 140

Cys Leu Arg Cys Pro Cys Ser Ala Val Thr Ser Thr Gly Ser Cys Ser  
 145 150 155 160

Ile Lys Ser Ser Glu Leu Glu Pro Glu Cys Asp Gln Cys Lys Asp Gly  
 165 170 175

Tyr Ile Gly Pro Asn Cys Asn Lys Cys Glu Asn Gly Tyr Tyr Asn Phe  
 180 185 190

Asp Ser Ile Cys Arg Lys Cys Gln Cys His Gly His Val Asp Pro Val  
 195 200 205

Lys Thr Pro Lys Ile Cys Lys Pro Glu Ser Gly Glu Cys Ile Asn Cys  
 210 215 220

Leu His Asn Thr Thr Gly Phe Trp Cys Glu Asn Cys Leu Glu Gly Tyr  
 225 230 235 240

Val His Asp Leu Glu Gly Asn Cys Ile Lys Lys Glu Val Ile Leu Pro  
 245 250 255

Thr Pro Glu Gly Ser Thr Ile Leu Val Ser Asn Ala Ser Leu Thr Thr  
 260 265 270

Ser Val Pro Thr Pro Val Ile Asn Ser Thr Phe Thr Pro Thr Thr Leu  
 275 280 285

Gln Thr Ile Phe Ser Val Ser Thr Ser Glu Asn Ser Thr Ser Ala Leu  
 290 295 300

Ala Asp Val Ser Trp Thr Gln Phe Asn Ile Ile Ile Leu Thr Val Ile  
 305 310 315 320

Ile Ile Val Val Val Leu Leu Met Gly Phe Val Gly Ala Val Tyr Met  
 325 330 335

Tyr Arg Glu Tyr Gln Asn Arg Lys Leu Asn Ala Pro Phe Trp Thr Ile  
 340 345 350

Glu Leu Lys Glu Asp Asn Ile Ser Phe Ser Ser Tyr His Asp Ser Ile

355

360

365

Pro Asn Ala Asp Val Ser Gly Leu Leu Glu Asp Asp Gly Asn Glu Val  
 370 375 380

Ala Pro Asn Gly Gln Leu Thr Leu Thr Thr Pro Ile His Asn Tyr Lys  
 385 390 395 400

Ala

<210> 225  
 <211> 686  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 225

Met Lys Pro Ser Trp Leu Gln Cys Arg Lys Val Thr Ser Ala Gly Gly  
 1 5 10 15

Leu Gly Gly Pro Leu Pro Gly Ser Ser Pro Ala Arg Gly Ala Gly Ala  
 20 25 30

Ala Leu Arg Ala Leu Val Val Pro Gly Pro Arg Gly Gly Leu Gly Gly  
 35 40 45

Arg Gly Cys Arg Ala Leu Ser Ser Gly Ser Gly Ser Glu Tyr Lys Thr  
 50 55 60

His Phe Ala Ala Ser Val Thr Asp Pro Glu Arg Phe Trp Gly Lys Ala  
 65 70 75 80

Ala Glu Gln Ile Ser Trp Tyr Lys Pro Trp Thr Lys Thr Leu Glu Asn  
 85 90 95

Lys His Ser Pro Ser Thr Arg Trp Phe Val Glu Gly Met Leu Asn Ile  
 100 105 110

Cys Tyr Asn Ala Val Asp Arg His Ile Glu Asn Gly Lys Gly Asp Lys  
 115 120 125

Ile Ala Ile Ile Tyr Asp Ser Pro Val Thr Asn Thr Lys Ala Thr Phe  
 130 135 140

Thr Tyr Lys Glu Val Leu Glu Gln Val Ser Lys Leu Ala Gly Val Leu  
 145 150 155 160

Val Lys His Gly Ile Lys Lys Gly Asp Thr Val Val Ile Tyr Met Pro  
 165 170 175

Met Ile Pro Gln Ala Met Tyr Thr Met Leu Ala Cys Ala Arg Ile Gly  
 180 185 190

Ala Ile His Ser Leu Ile Phe Gly Gly Phe Ala Ser Lys Glu Leu Ser  
 195 200 205

Ser Arg Ile Asp His Val Lys Pro Lys Val Val Val Thr Ala Ser Phe  
 210 215 220

Gly Ile Glu Pro Gly Arg Arg Val Glu Tyr Val Pro Leu Val Glu Glu  
 225 230 235 240

Ala Leu Lys Ile Gly Gln His Lys Pro Asp Lys Ile Leu Ile Tyr Asn  
 245 250 255

Arg Pro Asn Met Glu Ala Val Pro Leu Ala Pro Gly Arg Asp Leu Asp  
 260 265 270

Trp Asp Glu Glu Met Ala Lys Ala Gln Ser His Asp Cys Val Pro Val  
 275 280 285

Leu Ser Glu His Pro Leu Tyr Ile Leu Tyr Thr Ser Gly Thr Thr Gly  
 290 295 300

Leu Pro Lys Gly Val Ile Arg Pro Thr Gly Gly Tyr Ala Val Met Leu  
 305 310 315 320

His Trp Ser Met Ser Ser Ile Tyr Gly Leu Gln Pro Gly Glu Val Trp  
 325 330 335

Trp Ala Ala Ser Asp Leu Gly Trp Val Val Gly His Ser Tyr Ile Cys  
 340 345 350

Tyr Gly Pro Leu Leu His Gly Asn Thr Thr Val Leu Tyr Glu Gly Lys  
 355 360 365



Pro Val Gly Thr Pro Asp Ala Gly Ala Tyr Phe Arg Val Leu Ala Glu  
370 375 380

His Gly Val Ala Ala Leu Phe Thr Ala Pro Thr Ala Ile Arg Ala Ile  
385 390 395 400

Arg Gln Gln Asp Pro Gly Ala Ala Leu Gly Lys Gln Tyr Ser Leu Thr  
405 410 415

Arg Phe Lys Thr Leu Phe Val Ala Gly Glu Arg Cys Asp Val Glu Thr  
420 425 430

Leu Glu Trp Ser Lys Asn Val Phe Arg Val Pro Val Leu Asp His Trp  
435 440 445

Trp Gln Thr Glu Thr Gly Ser Pro Ile Thr Ala Ser Cys Val Gly Leu  
450 455 460

Gly Asn Ser Lys Thr Pro Pro Pro Gly Gln Ala Gly Lys Ser Val Pro  
465 470 475 480

Gly Tyr Asn Val Met Ile Leu Asp Asp Asn Met Gln Lys Leu Lys Ala  
485 490 495

Arg Cys Leu Gly Asn Ile Val Val Lys Leu Pro Leu Pro Pro Gly Ala  
500 505 510

Phe Ser Gly Leu Trp Lys Asn Gln Glu Ala Phe Lys His Leu Tyr Phe  
515 520 525

Glu Lys Phe Pro Gly Tyr Tyr Asp Thr Met Asp Ala Gly Tyr Met Asp  
530 535 540

Glu Glu Gly Tyr Leu Tyr Val Met Ser Arg Val Asp Asp Val Ile Asn  
545 550 555 560

Val Ala Gly His Arg Ile Ser Ala Gly Ala Ile Glu Glu Ser Ile Leu  
565 570 575

Ser His Gly Thr Val Ala Asp Cys Ala Val Val Gly Lys Glu Asp Pro  
580 585 590

Leu Lys Gly His Val Pro Leu Ala Leu Cys Val Leu Arg Lys Asp Ile

595

600

605

Asn Ala Thr Glu Glu Gln Val Leu Glu Glu Ile Val Lys His Val Arg  
 610 615 620

Gln Asn Ile Gly Pro Val Ala Ala Phe Arg Asn Ala Val Phe Val Lys  
 625 630 635 640

Gln Leu Pro Lys Thr Arg Ser Gly Lys Ile Pro Arg Ser Ala Leu Ser  
 645 650 655

Ala Ile Val Asn Gly Lys Pro Tyr Lys Ile Thr Ser Thr Ile Glu Asp  
 660 665 670

Pro Ser Ile Phe Gly His Val Glu Glu Met Leu Lys Gln Ala  
 675 680 685

<210> 226  
 <211> 225  
 <212> PRT  
 <213> Homo sapiens

<400> 226

Met Ala Ala Ala Gly Gly Gly Gly Gly Gly Ala Ala Ala Ala Gly Arg  
 1 5 10 15

Ala Tyr Ser Phe Lys Val Val Leu Leu Gly Glu Gly Cys Val Gly Lys  
 20 25 30

Thr Ser Leu Val Leu Arg Tyr Cys Glu Asn Lys Phe Asn Asp Lys His  
 35 40 45

Ile Thr Thr Leu Gln Ala Ser Phe Leu Thr Lys Lys Leu Asn Ile Gly  
 50 55 60

Gly Lys Arg Val Asn Leu Ala Ile Trp Asp Thr Ala Gly Gln Glu Arg  
 65 70 75 80

Phe His Ala Leu Gly Pro Ile Tyr Tyr Arg Asp Ser Asn Gly Ala Ile  
 85 90 95

Leu Val Tyr Asp Ile Thr Asp Glu Asp Ser Phe Gln Lys Val Lys Asn  
 100 105 110

Trp Val Lys Glu Leu Arg Lys Met Leu Gly Asn Glu Ile Cys Leu Cys  
 115 120 125

Ile Val Gly Asn Lys Ile Asp Leu Glu Lys Glu Arg His Val Ser Ile  
 130 135 140

Gln Glu Ala Glu Ser Tyr Ala Glu Ser Val Gly Ala Lys His Tyr His  
 145 150 155 160

Thr Ser Ala Lys Gln Asn Lys Gly Ile Glu Glu Leu Phe Leu Asp Leu  
 165 170 175

Cys Lys Arg Met Ile Glu Thr Ala Gln Val Asp Glu Arg Ala Lys Gly  
 180 185 190

Asn Gly Ser Ser Gln Pro Gly Thr Ala Arg Arg Gly Val Gln Ile Ile  
 195 200 205

Asp Asp Glu Pro Gln Ala Gln Thr Ser Gly Gly Gly Cys Cys Ser Ser  
 210 215 220

Gly  
 225

<210> 227  
 <211> 380  
 <212> PRT  
 <213> Homo sapiens

<400> 227

Met Gly Ser Thr Asp Ser Lys Leu Asn Phe Arg Lys Ala Val Ile Gln  
 1 5 10 15

Leu Thr Thr Lys Thr Gln Pro Val Glu Ala Thr Asp Asp Ala Phe Trp  
 20 25 30

Asp Gln Phe Trp Ala Asp Thr Ala Thr Ser Val Gln Asp Val Phe Ala  
 35 40 45

Leu Val Pro Ala Ala Glu Ile Arg Ala Val Arg Glu Glu Ser Pro Ser  
 50 55 60

Asn Leu Ala Thr Leu Cys Tyr Lys Ala Val Glu Lys Leu Val Gln Gly

65		70		75		80									
Ala	Glu	Ser	Gly	Cys	His	Ser	Glu	Lys	Glu	Lys	Gln	Ile	Val	Leu	Asn
			85					90						95	
Cys	Ser	Arg	Leu	Leu	Thr	Arg	Val	Leu	Pro	Tyr	Ile	Phe	Glu	Asp	Pro
			100					105					110		
Asp	Trp	Arg	Gly	Phe	Phe	Trp	Ser	Thr	Val	Pro	Gly	Ala	Gly	Arg	Gly
		115					120					125			
Gly	Gly	Glu	Glu	Asp	Asp	Glu	His	Ala	Arg	Pro	Leu	Ala	Glu	Ser	Leu
	130					135					140				
Leu	Leu	Ala	Ile	Ala	Asp	Leu	Leu	Phe	Cys	Pro	Asp	Phe	Thr	Val	Gln
145					150					155					160
Ser	His	Arg	Arg	Ser	Thr	Val	Asp	Ser	Ala	Glu	Asp	Val	His	Ser	Leu
				165					170					175	
Asp	Ser	Cys	Glu	Tyr	Ile	Trp	Glu	Ala	Gly	Val	Gly	Phe	Ala	His	Ser
			180					185					190		
Pro	Gln	Pro	Asn	Tyr	Ile	His	Asp	Met	Asn	Arg	Met	Glu	Leu	Leu	Lys
		195					200					205			
Leu	Leu	Leu	Thr	Cys	Phe	Ser	Glu	Ala	Met	Tyr	Leu	Pro	Pro	Ala	Pro
	210					215					220				
Glu	Ser	Gly	Ser	Thr	Asn	Pro	Trp	Val	Gln	Phe	Phe	Cys	Ser	Thr	Glu
225					230					235					240
Asn	Arg	His	Ala	Leu	Pro	Leu	Phe	Thr	Ser	Leu	Leu	Asn	Thr	Val	Cys
				245					250					255	
Ala	Tyr	Asp	Pro	Val	Gly	Tyr	Gly	Ile	Pro	Tyr	Asn	His	Leu	Leu	Phe
			260					265					270		
Ser	Asp	Tyr	Arg	Glu	Pro	Leu	Val	Glu	Glu	Ala	Ala	Gln	Val	Leu	Ile
		275					280					285			
Val	Thr	Leu	Asp	His	Asp	Ser	Ala	Ser	Ser	Ala	Ser	Pro	Thr	Val	Asp
	290					295					300				

Gly Thr Thr Thr Gly Thr Ala Met Asp Asp Ala Asp Pro Pro Gly Pro  
305 310 315 320

Glu Asn Leu Phe Val Asn Tyr Leu Ser Arg Ile His Arg Glu Glu Asp  
325 330 335

Phe Gln Phe Ile Leu Lys Gly Ile Ala Arg Leu Leu Ser Asn Leu Leu  
340 345 350

Leu Gln Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys  
355 360 365

Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys  
370 375 380

<210> 228  
<211> 144  
<212> PRT  
<213> Homo sapiens

<400> 228

Met Cys Arg Val Gln Thr His Gly Cys His Pro Leu Arg Ser Val Thr  
1 5 10 15

Val Arg Pro Asp Pro Ser Pro Ala Ala Pro Pro Pro His Pro Gly Pro  
20 25 30

Pro Arg Gln Leu Ser Gln Gly Ala Gln Ala Cys Leu Ala Pro Gln Pro  
35 40 45

Ser Gly Asn Pro Ala Arg Arg Pro Leu Gln Val Gly Ser Gly Pro Gln  
50 55 60

Val Ala Lys Gln Arg Gln Gln Gln Pro Arg Leu Thr Pro Cys Pro Ser  
65 70 75 80

Leu Trp Arg Pro Gly Thr Pro Ala Ile Ser Thr Thr Trp Val Arg Leu  
85 90 95

Ser Leu Ser Gly Ser Pro Ala Arg Val Pro Pro Gly Val Leu Gly His  
100 105 110

Leu Arg Gly Ser Leu Met Gly Gln Ala Gly Gln Ser Glu Leu Arg Ala  
 115 120 125

Leu Ser Gly Trp Cys Pro Asn Leu Ser Thr Pro His Ser Phe Pro Pro  
 130 135 140

<210> 229  
 <211> 141  
 <212> PRT  
 <213> Homo sapiens

<400> 229

Met Thr Lys Gln His Glu Leu Gly Gly Leu Leu Ala Leu Val Gln Asn  
 1 5 10 15

Cys Gln Ser Glu Met Asn Ile Lys Asp Ser Arg Ala Val Gly Leu Ser  
 20 25 30

Val Lys Arg Leu Cys Ile Ser Phe Val Asp Glu Phe Cys Glu Arg Thr  
 35 40 45

Glu Arg Pro Leu Tyr Leu Ala Gln Gly Leu Phe Met Lys Arg Glu Thr  
 50 55 60

Tyr Trp Glu Val Gln Asp Ser Gly Ile Ser Pro Leu Leu Leu Leu Leu  
 65 70 75 80

Ser Thr Ala Leu Asp Cys Ser Pro Glu Ala Glu Thr Arg Gln Ser Pro  
 85 90 95

Gly Gly Arg Lys Met Leu Gln Glu Pro Thr Leu Ser Met Ser Leu Gln  
 100 105 110

Ile Leu Thr Gly Phe Leu Trp Val Gln Leu Trp Asn Trp Glu Thr Phe  
 115 120 125

Leu Arg Ile Arg Thr His Ser Thr Asp Ala Ser Cys Pro  
 130 135 140

<210> 230  
 <211> 161  
 <212> PRT  
 <213> Homo sapiens

<400> 230

Met Ser Tyr Leu Ser Gly Ser Ser Ala Ser Pro Ala Arg Arg Leu Gly  
1 5 10 15

Val Val Lys Val Val Pro Arg Pro Cys Leu Gln Trp Leu Glu Asn Pro  
20 25 30

Gly Gly Cys Leu Gly Pro Ser Gly Gln Arg Glu Ala Gly Ser Ser Ser  
35 40 45

Pro Gly Asp Cys Gly His Ile Gly Ala Cys Leu Gly Leu Glu Gly Gln  
50 55 60

Val Thr Ser Pro Ala Thr Leu Pro Ser Leu Leu Trp Gly Pro His Phe  
65 70 75 80

Arg Ala Thr Leu Pro Glu Ala His Ala Ser Ile His Ser Phe Ser Ala  
85 90 95

Leu Asn Leu Ile His Lys Gln Pro Pro Pro Phe Pro Phe Pro Ser His  
100 105 110

Ser Val Asp Val Ile Leu Pro Pro Pro Val Ser Ile Leu Arg Gln Ala  
115 120 125

Ser Lys Glu Ala Leu Thr Leu Leu Pro Lys Trp Cys Phe Leu Lys Asn  
130 135 140

Thr Ile Thr Thr Leu Gly Ala Ile Phe Ser His Leu Pro Val Phe Arg  
145 150 155 160

Met

<210> 231  
<211> 132  
<212> PRT  
<213> Homo sapiens

<400> 231

Met Arg Ala Ile Asn Ile Ala Asp Glu Leu Pro Arg Ser Arg Ala Arg  
1 5 10 15

Lys Leu Ala Asp Glu Gln Leu Ser Ser Val Ile Gln Asp Met Ala Val

20

25

30

Arg Gln His Leu Leu Thr Asn Leu Val Glu Val Asp Gly Arg Phe Val  
 35 40 45

Trp Arg Val Asn Leu Asp Ala Leu Thr Gln His Leu Asp Lys Ile Leu  
 50 55 60

Ala Phe Pro Gln Arg Gln Glu Ser Tyr Leu Gly Pro Thr Leu Phe Leu  
 65 70 75 80

Leu Gly Gly Asn Ser Gln Phe Val His Pro Ser His His Pro Glu Ile  
 85 90 95

Met Arg Leu Phe Pro Arg Ala Gln Met Gln Thr Val Pro Asn Ala Gly  
 100 105 110

His Trp Ile His Ala Asp Arg Pro Gln Asp Phe Ile Ala Ala Ile Arg  
 115 120 125

Gly Phe Leu Val  
 130

<210> 232

<211> 328

<212> PRT

<213> Homo sapiens

<400> 232

Met Leu Pro Arg Val Gly Cys Pro Ala Leu Pro Leu Pro Pro Pro Pro  
 1 5 10 15

Leu Leu Pro Leu Leu Pro Leu Leu Leu Leu Leu Gly Ala Ser Gly  
 20 25 30

Gly Gly Gly Gly Ala Arg Ala Glu Val Leu Phe Arg Cys Pro Pro Cys  
 35 40 45

Thr Pro Glu Arg Leu Ala Ala Cys Gly Pro Pro Pro Val Ala Pro Pro  
 50 55 60

Ala Ala Val Ala Ala Val Ala Gly Gly Ala Arg Met Pro Cys Ala Glu  
 65 70 75 80



Leu Val Arg Glu Pro Gly Cys Gly Cys Cys Ser Val Cys Ala Arg Leu  
                     85                    90                    95

Glu Gly Glu Ala Cys Gly Val Tyr Thr Pro Arg Cys Gly Gln Gly Leu  
                     100                    105                    110

Arg Cys Tyr Pro His Pro Gly Ser Glu Leu Pro Leu Gln Ala Leu Val  
                     115                    120                    125

Met Gly Glu Gly Thr Cys Glu Lys Arg Arg Asp Ala Glu Tyr Gly Ala  
                     130                    135                    140

Ser Pro Glu Gln Val Ala Asp Asn Gly Asp Asp His Ser Glu Gly Gly  
                     145                    150                    155                    160

Leu Val Glu Asn His Val Asp Ser Thr Met Asn Met Leu Gly Gly Gly  
                     165                    170                    175

Gly Ser Ala Gly Arg Lys Pro Leu Lys Ser Gly Met Lys Glu Leu Ala  
                     180                    185                    190

Val Phe Arg Glu Lys Val Thr Glu Gln His Arg Gln Met Gly Lys Gly  
                     195                    200                    205

Gly Lys His His Leu Gly Leu Glu Glu Pro Lys Lys Leu Arg Pro Pro  
                     210                    215                    220

Pro Ala Arg Thr Pro Cys Gln Gln Glu Leu Asp Gln Val Leu Glu Arg  
                     225                    230                    235                    240

Ile Ser Thr Met Arg Leu Pro Asp Glu Arg Gly Pro Leu Glu His Leu  
                     245                    250                    255

Tyr Ser Leu His Ile Pro Asn Cys Asp Lys His Gly Leu Tyr Asn Leu  
                     260                    265                    270

Lys Gln Cys Lys Met Ser Leu Asn Gly Gln Arg Gly Glu Cys Trp Cys  
                     275                    280                    285

Val Asn Pro Asn Thr Gly Lys Leu Ile Gln Gly Ala Pro Thr Ile Arg  
                     290                    295                    300

Gly Asp Pro Glu Cys His Leu Phe Tyr Asn Glu Gln Gln Glu Ala Cys  
 305 310 315 320

Gly Val His Thr Gln Arg Met Gln  
 325

<210> 233  
 <211> 417  
 <212> PRT  
 <213> Homo sapiens

<400> 233

Met Ala Val Glu Thr Thr Val His Thr His Leu Ser Ala Ser Pro Pro  
 1 5 10 15

Gln Gly Ser Pro Tyr Asp His Thr Pro Gly Met Ala Gly Ser Leu Gly  
 20 25 30

Tyr His Pro Tyr Ala Ala Pro Leu Gly Ser Tyr Pro Tyr Gly Asp Pro  
 35 40 45

Ala Tyr Arg Lys Asn Ala Thr Arg Asp Ala Thr Ala Thr Leu Lys Ala  
 50 55 60

Trp Leu Asn Glu His Arg Lys Asn Pro Tyr Pro Thr Lys Gly Glu Lys  
 65 70 75 80

Ile Met Leu Ala Ile Ile Thr Lys Met Thr Leu Thr Gln Val Ser Thr  
 85 90 95

Trp Phe Ala Asn Ala Arg Arg Arg Leu Lys Lys Glu Asn Lys Met Thr  
 100 105 110

Trp Thr Pro Arg Asn Arg Ser Glu Asp Glu Glu Glu Glu Glu Asn Ile  
 115 120 125

Asp Leu Glu Lys Asn Asp Glu Asp Glu Pro Gln Lys Pro Glu Asp Lys  
 130 135 140

Gly Asp Pro Glu Gly Pro Glu Ala Gly Gly Ala Glu Gln Lys Ala Ala  
 145 150 155 160

Ser Gly Cys Glu Arg Leu Gln Gly Pro Pro Thr Pro Ala Gly Lys Glu  
 165 170 175

Thr Glu Gly Ser Leu Ser Asp Ser Asp Phe Lys Glu Pro Pro Ser Glu  
 180 185 190

Gly Arg Leu Asp Ala Leu Gln Gly Pro Pro Arg Thr Gly Gly Pro Ser  
 195 200 205

Pro Ala Gly Pro Ala Ala Ala Arg Leu Ala Glu Asp Pro Ala Pro His  
 210 215 220

Tyr Pro Ala Gly Ala Pro Ala Pro Gly Pro His Pro Ala Ala Gly Glu  
 225 230 235 240

Val Pro Pro Gly Pro Gly Gly Pro Ser Val Ile His Ser Pro Pro Pro  
 245 250 255

Pro Pro Pro Pro Ala Val Leu Ala Lys Pro Lys Leu Trp Ser Leu Ala  
 260 265 270

Glu Ile Ala Thr Leu Ser Asp Lys Val Lys Asp Gly Gly Gly Gly Asn  
 275 280 285

Glu Gly Ser Pro Cys Pro Pro Cys Pro Gly Pro Ile Ala Gly Gln Ala  
 290 295 300

Leu Gly Gly Ser Arg Ala Ser Pro Ala Pro Ala Pro Ser Arg Ser Pro  
 305 310 315 320

Ser Ala Gln Cys Pro Phe Pro Gly Gly Thr Val Leu Ser Arg Pro Leu  
 325 330 335

Tyr Tyr Thr Ala Pro Phe Tyr Pro Gly Tyr Thr Asn Tyr Gly Ser Phe  
 340 345 350

Gly His Leu His Gly His Pro Gly Pro Gly Pro Gly Pro Thr Thr Gly  
 355 360 365

Pro Gly Ser His Phe Asn Gly Leu Asn Gln Thr Val Leu Asn Arg Ala  
 370 375 380

Asp Ala Leu Ala Lys Asp Pro Lys Met Leu Arg Ser Gln Ser Gln Leu  
 385 390 395 400

Asp Leu Cys Lys Asp Ser Pro Tyr Glu Leu Lys Lys Gly Met Ser Asp  
 405 410 415

Ile

<210> 234  
 <211> 257  
 <212> PRT  
 <213> Homo sapiens

<400> 234

Met Ser Gly His Lys Cys Ser Tyr Pro Trp Asp Leu Gln Asp Arg Tyr  
 1 5 10 15

Ala Gln Asp Lys Ser Val Val Asn Lys Met Gln Gln Lys Tyr Trp Glu  
 20 25 30

Thr Lys Gln Ala Phe Ile Lys Ala Thr Gly Lys Lys Glu Asp Glu His  
 35 40 45

Val Val Ala Ser Asp Ala Asp Leu Asp Ala Lys Leu Glu Leu Phe His  
 50 55 60

Ser Ile Gln Arg Thr Cys Leu Asp Leu Ser Lys Ala Ile Val Leu Tyr  
 65 70 75 80

Gln Lys Arg Ile Cys Phe Leu Ser Gln Glu Glu Asn Glu Leu Gly Lys  
 85 90 95

Phe Leu Arg Ser Gln Gly Phe Gln Asp Lys Thr Arg Ala Gly Lys Met  
 100 105 110

Met Gln Ala Thr Gly Lys Ala Leu Cys Phe Ser Ser Gln Gln Arg Leu  
 115 120 125

Ala Leu Arg Asn Pro Leu Cys Arg Phe His Gln Glu Val Glu Thr Phe  
 130 135 140

Arg His Arg Ala Ile Ser Asp Thr Trp Leu Thr Val Asn Arg Met Glu  
 145 150 155 160

Gln Cys Arg Thr Glu Tyr Arg Gly Ala Leu Leu Trp Met Lys Asp Val

165                                      170                                      175  
 Ser Gln Glu Leu Asp Pro Asp Leu Tyr Lys Gln Met Glu Lys Phe Arg  
    180                                      185                                      190  
 Lys Val Gln Thr Gln Val Arg Leu Ala Lys Lys Asn Phe Asp Lys Leu  
    195                                      200                                      205  
 Lys Met Asp Val Cys Gln Lys Val Asp Leu Leu Gly Ala Ser Arg Cys  
    210                                      215                                      220  
 Asn Leu Leu Ser His Met Leu Ala Thr Tyr Gln Leu Ala Trp Asp Gln  
    225                                      230                                      235                                      240  
 Trp Gln Gly Pro Arg Asn Leu Lys Val Leu Thr Lys Met Thr Cys Cys  
    245                                      250                                      255  
 Cys

<210> 235  
 <211> 395  
 <212> PRT  
 <213> Homo sapiens

<400> 235

Met Asp Leu Gly Ile Pro Asp Leu Leu Asp Ala Trp Leu Glu Pro Pro  
 1                                      5                                      10                                      15  
 Glu Asp Ile Phe Ser Thr Gly Ser Val Leu Glu Leu Gly Leu His Cys  
    20                                      25                                      30  
 Pro Pro Leu Glu Val Pro Val Thr Arg Leu Gln Glu Gln Gly Leu Gln  
    35                                      40                                      45  
 Gly Trp Lys Ser Gly Gly Asp Arg Gly Cys Gly Leu Gln Glu Ser Glu  
    50                                      55                                      60  
 Pro Glu Asp Phe Leu Lys Leu Phe Ile Asp Pro Asn Glu Val Tyr Cys  
 65                                      70                                      75                                      80  
 Ser Glu Ala Ser Pro Gly Ser Asp Ser Gly Ile Ser Glu Asp Pro Cys  
    85                                      90                                      95

His Pro Asp Ser Pro Pro Ala Pro Arg Ala Thr Ser Ser Pro Met Leu  
 100 105 110

Tyr Glu Val Val Tyr Glu Ala Gly Ala Leu Glu Arg Met Gln Gly Glu  
 115 120 125

Thr Gly Pro Asn Val Gly Leu Ile Ser Ile Gln Leu Asp Gln Trp Ser  
 130 135 140

Pro Ala Phe Met Val Pro Asp Ser Cys Met Val Ser Glu Leu Pro Phe  
 145 150 155 160

Asp Ala His Ala His Ile Leu Pro Arg Ala Gly Thr Val Ala Pro Val  
 165 170 175

Pro Cys Thr Thr Leu Leu Pro Cys Gln Thr Leu Phe Leu Thr Asp Glu  
 180 185 190

Glu Lys Arg Leu Leu Gly Gln Glu Gly Val Ser Leu Pro Ser His Leu  
 195 200 205

Pro Leu Thr Lys Ala Glu Glu Arg Val Leu Lys Lys Val Arg Arg Lys  
 210 215 220

Ile Arg Asn Lys Gln Ser Ala Gln Asp Ser Arg Arg Arg Lys Lys Glu  
 225 230 235 240

Tyr Ile Asp Gly Leu Glu Ser Arg Val Ala Ala Cys Ser Ala Gln Asn  
 245 250 255

Gln Glu Leu Gln Lys Lys Val Gln Glu Leu Glu Arg His Asn Ile Ser  
 260 265 270

Leu Val Ala Gln Leu Arg Gln Leu Gln Thr Leu Ile Ala Gln Thr Ser  
 275 280 285

Asn Lys Ala Ala Gln Thr Ser Thr Cys Val Leu Ile Leu Leu Phe Ser  
 290 295 300

Leu Ala Leu Ile Ile Leu Pro Ser Phe Ser Pro Phe Gln Ser Arg Pro  
 305 310 315 320



Glu Gly Leu Lys Leu Ile Ser Asp Ile Ile Arg Glu Lys Met Gly Ile  
130 135 140

Asp Ile Ser Val Leu Met Gly Ala Asn Ile Ala Asn Glu Val Ala Ala  
145 150 155 160

Glu Lys Phe Cys Glu Thr Thr Ile Gly Ser Lys Val Met Glu Asn Gly  
165 170 175

Leu Leu Phe Lys Glu Leu Leu Gln Thr Pro Asn Phe Arg Ile Thr Val  
180 185 190

Val Asp Asp Ala Asp Thr Val Glu Leu Cys Gly Ala Leu Lys Asn Ile  
195 200 205

Val Ala Val Gly Ala Gly Phe Cys Asp Gly Leu Arg Cys Gly Asp Asn  
210 215 220

Thr Lys Ala Ala Val Ile Arg Leu Gly Leu Met Glu Met Ile Ala Phe  
225 230 235 240

Ala Arg Ile Phe Cys Lys Gly Gln Val Ser Thr Ala Thr Phe Leu Glu  
245 250 255

Ser Cys Gly Val Ala Asp Leu Ile Thr Thr Cys Tyr Gly Gly Arg Asn  
260 265 270

Arg Arg Val Ala Glu Ala Phe Ala Arg Thr Gly Lys Thr Ile Glu Glu  
275 280 285

Leu Glu Lys Glu Met Leu Asn Gly Gln Lys Leu Gln Gly Pro Gln Thr  
290 295 300

Ser Ala Glu Val Tyr Arg Ile Leu Lys Gln Lys Gly Leu Leu Asp Lys  
305 310 315 320

Phe Pro Leu Phe Thr Ala Val Tyr Gln Ile Cys Tyr Glu Ser Arg Pro  
325 330 335

Val Gln Glu Met Leu Ser Cys Leu Gln Ser His Pro Glu His Thr  
340 345 350



<210> 237  
 <211> 871  
 <212> PRT  
 <213> Homo sapiens

<400> 237

Met Asp Leu Lys Leu Arg Ala Ala Ser Pro Ile Ile Thr Leu Val Ala  
 1 5 10 15

Leu Asp Glu Ala Leu Asp Asn Tyr Thr Ile Thr Phe Leu Ile Arg Gly  
 20 25 30

Val Ala Ile Gly Gln Thr Ser Leu Thr Ala Ser Val Thr Asn Lys Ala  
 35 40 45

Gly Gln Arg Ile Asn Ser Ala Pro Gln Gln Ile Glu Val Phe Pro Pro  
 50 55 60

Phe Arg Leu Met Pro Arg Lys Val Thr Leu Leu Ile Gly Ala Thr Met  
 65 70 75 80

Gln Val Thr Ser Glu Gly Gly Pro Gln Pro Gln Ser Asn Ile Leu Phe  
 85 90 95

Ser Ile Ser Asn Glu Ser Val Ala Leu Val Ser Ala Ala Gly Leu Val  
 100 105 110

Gln Gly Leu Ala Ile Gly Asn Gly Thr Val Ser Gly Leu Val Gln Ala  
 115 120 125

Val Asp Ala Glu Thr Gly Lys Val Val Ile Ile Ser Gln Asp Leu Val  
 130 135 140

Gln Val Glu Val Leu Leu Leu Arg Ala Val Arg Ile Arg Ala Pro Ile  
 145 150 155 160

Met Arg Met Arg Thr Gly Thr Gln Met Pro Ile Tyr Val Thr Gly Ile  
 165 170 175

Thr Asn His Gln Asn Pro Phe Ser Phe Gly Asn Ala Val Pro Gly Leu  
 180 185 190

Thr Phe His Trp Ser Val Thr Lys Arg Asp Val Leu Asp Leu Arg Gly

195	200	205
Arg His His Glu Ala Ser Ile Arg Leu Pro Ser Gln Tyr Asn Phe Ala		
210	215	220
Met Asn Val Leu Gly Arg Val Lys Gly Arg Thr Gly Leu Arg Val Val		
225	230	235
Val Lys Ala Val Asp Pro Thr Ser Gly Gln Leu Tyr Gly Leu Ala Arg		
	245	250
		255
Glu Leu Ser Asp Glu Ile Gln Val Gln Val Phe Glu Lys Leu Gln Leu		
	260	265
		270
Leu Asn Pro Glu Ile Glu Ala Glu Gln Ile Leu Met Ser Pro Asn Ser		
	275	280
		285
Tyr Ile Lys Leu Gln Thr Asn Arg Asp Gly Ala Ala Ser Leu Ser Tyr		
290	295	300
Arg Val Leu Asp Gly Pro Glu Lys Val Pro Val Val His Val Asp Glu		
305	310	315
		320
Lys Gly Phe Leu Ala Ser Gly Ser Met Ile Gly Thr Ser Thr Ile Glu		
	325	330
		335
Val Ile Ala Gln Glu Pro Phe Gly Ala Asn Gln Thr Ile Ile Val Ala		
	340	345
		350
Val Lys Val Ser Pro Val Ser Tyr Leu Arg Val Ser Met Ser Pro Val		
	355	360
		365
Leu His Thr Gln Asn Lys Glu Ala Leu Val Ala Val Pro Leu Gly Met		
370	375	380
Thr Val Thr Phe Thr Val His Phe His Asp Asn Ser Gly Asp Val Phe		
385	390	395
		400
His Ala His Ser Ser Val Leu Asn Phe Ala Thr Asn Arg Asp Asp Phe		
	405	410
		415
Val Gln Ile Gly Lys Gly Pro Thr Asn Asn Thr Cys Val Val Arg Thr		
	420	425
		430

Val Ser Val Gly Leu Thr Leu Leu Arg Val Trp Asp Ala Glu His Pro  
 435 440 445

Gly Leu Ser Asp Phe Met Pro Leu Pro Val Leu Gln Ala Ile Ser Pro  
 450 455 460

Glu Leu Ser Gly Ala Met Val Val Gly Asp Val Leu Cys Leu Ala Thr  
 465 470 475 480

Val Leu Thr Ser Leu Glu Gly Leu Ser Gly Thr Trp Ser Ser Ser Ala  
 485 490 495

Asn Ser Ile Leu His Ile Asp Pro Lys Thr Gly Val Ala Val Ala Arg  
 500 505 510

Ala Val Gly Ser Val Thr Val Tyr Tyr Glu Val Ala Gly His Leu Arg  
 515 520 525

Thr Tyr Lys Glu Val Val Val Ser Val Pro Gln Arg Ile Met Ala Arg  
 530 535 540

His Leu His Pro Ile Gln Thr Ser Phe Gln Glu Ala Thr Ala Ser Lys  
 545 550 555 560

Val Ile Val Ala Val Gly Asp Arg Ser Ser Asn Leu Arg Gly Glu Cys  
 565 570 575

Thr Pro Thr Gln Arg Glu Val Ile Gln Ala Leu His Pro Glu Thr Leu  
 580 585 590

Ile Ser Cys Gln Ser Gln Phe Lys Pro Ala Val Phe Asp Phe Pro Ser  
 595 600 605

Gln Asp Val Phe Thr Val Glu Pro Gln Phe Asp Thr Ala Leu Gly Gln  
 610 615 620

Tyr Phe Cys Ser Ile Thr Met His Arg Leu Thr Asp Lys Gln Arg Lys  
 625 630 635 640

His Leu Ser Met Lys Lys Thr Ala Leu Val Val Ser Ala Ser Leu Ser  
 645 650 655

Ser Ser His Phe Ser Thr Glu Gln Val Gly Ala Glu Val Pro Phe Ser  
 660 665 670

Pro Gly Leu Phe Ala Asp Gln Ala Glu Ile Leu Leu Ser Asn His Tyr  
 675 680 685

Thr Ser Ser Glu Ile Arg Val Phe Gly Ala Pro Glu Val Leu Glu Asn  
 690 695 700

Leu Glu Val Lys Ser Gly Ser Pro Ala Val Leu Ala Phe Ala Lys Glu  
 705 710 715 720

Lys Ser Phe Gly Trp Pro Ser Phe Ile Thr Tyr Thr Val Gly Val Leu  
 725 730 735

Asp Pro Ala Ala Gly Ser Gln Gly Pro Leu Ser Thr Thr Leu Thr Phe  
 740 745 750

Ser Ser Pro Val Thr Asn Gln Ala Ile Ala Ile Pro Val Thr Val Ala  
 755 760 765

Phe Val Val Asp Arg Arg Gly Pro Gly Pro Tyr Gly Ala Ser Leu Phe  
 770 775 780

Gln His Phe Leu Asp Ser Tyr Gln Val Met Phe Phe Thr Leu Phe Ala  
 785 790 795 800

Leu Leu Ala Gly Thr Ala Val Met Ile Ile Ala Tyr His Thr Val Cys  
 805 810 815

Thr Pro Arg Asp Leu Ala Val Pro Ala Ala Leu Thr Pro Arg Ala Ser  
 820 825 830

Pro Gly His Ser Pro His Tyr Phe Ala Ala Ser Ser Pro Thr Ser Pro  
 835 840 845

Asn Ala Leu Pro Pro Ala Arg Lys Ala Ser Pro Pro Ser Gly Leu Trp  
 850 855 860

Ser Pro Ala Tyr Ala Ser His  
 865 870

<210> 238  
 <211> 728  
 <212> PRT  
 <213> Homo sapiens

<400> 238

Leu Pro Ala Cys Arg Leu Cys His Arg Arg Glu His Gly Arg Thr Val  
 1 5 10 15

Cys Ser Gly Val Asp Thr Lys Leu Lys Phe Thr Leu Glu Pro Ser Leu  
 20 25 30

Gly Gln Asn Gly Phe Gln Gln Trp Tyr Asp Ala Leu Lys Ala Val Ala  
 35 40 45

Arg Leu Ser Thr Gly Ile Pro Lys Glu Trp Arg Arg Lys Val Trp Leu  
 50 55 60

Thr Leu Ala Asp His Tyr Leu His Ser Ile Ala Ile Asp Trp Asp Lys  
 65 70 75 80

Thr Met Arg Phe Thr Phe Asn Glu Arg Ser Asn Pro Asp Asp Asp Ser  
 85 90 95

Met Gly Ile Gln Ile Val Lys Asp Leu His Arg Thr Gly Cys Ser Ser  
 100 105 110

Tyr Cys Gly Gln Glu Ala Glu Gln Asp Arg Val Val Leu Lys Arg Val  
 115 120 125

Leu Leu Ala Tyr Ala Arg Trp Asn Lys Thr Val Gly Tyr Cys Gln Gly  
 130 135 140

Phe Asn Ile Leu Ala Ala Leu Ile Leu Glu Val Met Glu Gly Asn Glu  
 145 150 155 160

Gly Asp Ala Leu Lys Ile Met Ile Tyr Leu Ile Asp Lys Val Leu Pro  
 165 170 175

Glu Ser Tyr Phe Val Asn Asn Leu Arg Ala Leu Ser Val Asp Met Ala  
 180 185 190

Val Phe Arg Asp Leu Leu Arg Met Lys Leu Pro Glu Leu Ser Gln His  
 195 200 205

Leu Asp Thr Leu Gln Arg Thr Ala Asn Lys Glu Ser Gly Gly Gly Tyr  
 210 215 220

Glu Pro Pro Leu Thr Asn Val Phe Thr Met Gln Trp Phe Leu Thr Leu  
 225 230 235 240

Phe Ala Thr Cys Leu Pro Asn Gln Thr Val Leu Lys Ile Trp Asp Ser  
 245 250 255

Val Phe Phe Glu Gly Ser Glu Ile Ile Leu Arg Val Ser Leu Ala Ile  
 260 265 270

Trp Ala Lys Leu Gly Glu Gln Ile Glu Cys Cys Glu Thr Ala Asp Glu  
 275 280 285

Phe Tyr Ser Thr Met Gly Arg Leu Thr Gln Glu Met Leu Glu Asn Asp  
 290 295 300

Leu Leu Gln Ser His Glu Leu Met Gln Thr Val Tyr Ser Met Ala Pro  
 305 310 315 320

Phe Pro Phe Pro Gln Leu Ala Glu Leu Arg Glu Lys Tyr Thr Tyr Asn  
 325 330 335

Ile Thr Pro Phe Pro Ala Thr Val Lys Pro Thr Ser Val Ser Gly Arg  
 340 345 350

His Ser Lys Ala Arg Asp Ser Asp Glu Glu Asn Asp Pro Asp Asp Glu  
 355 360 365

Asp Ala Val Val Asn Ala Val Gly Cys Leu Gly Pro Phe Ser Gly Phe  
 370 375 380

Leu Ala Pro Glu Leu Gln Lys Tyr Gln Lys Gln Ile Lys Glu Pro Asn  
 385 390 395 400

Glu Glu Gln Ser Leu Arg Ser Asn Asn Ile Ala Glu Leu Ser Pro Gly  
 405 410 415

Ala Ile Asn Ser Cys Arg Ser Glu Tyr His Ala Ala Phe Asn Ser Met  
 420 425 430

Met Met Glu Arg Met Thr Thr Asp Ile Asn Ala Leu Lys Arg Gln Tyr  
 435 440 445

Ser Arg Ile Lys Lys Lys Gln Gln Gln Gln Val His Gln Val Tyr Ile  
 450 455 460

Arg Ala Asp Lys Gly Pro Val Thr Ser Ile Leu Pro Ser Gln Val Asn  
 465 470 475 480

Ser Ser Pro Val Ile Asn His Leu Leu Leu Gly Lys Lys Met Lys Met  
 485 490 495

Thr Asn Arg Ala Ala Lys Asn Ala Val Ile His Ile Pro Gly His Thr  
 500 505 510

Gly Gly Lys Ile Ser Pro Val Pro Tyr Glu Asp Leu Lys Thr Lys Leu  
 515 520 525

Asn Ser Pro Trp Arg Thr His Ile Arg Val His Lys Lys Asn Met Pro  
 530 535 540

Arg Thr Lys Ser His Pro Gly Cys Gly Asp Thr Val Gly Leu Ile Asp  
 545 550 555 560

Glu Gln Asn Glu Ala Ser Lys Thr Asn Gly Leu Gly Ala Ala Glu Ala  
 565 570 575

Phe Pro Ser Gly Cys Thr Ala Thr Ala Gly Arg Glu Gly Ser Ser Pro  
 580 585 590

Glu Gly Ser Thr Arg Arg Thr Ile Glu Gly Gln Ser Pro Glu Pro Val  
 595 600 605

Phe Gly Asp Ala Asp Val Asp Val Ser Ala Val Gln Ala Lys Leu Gly  
 610 615 620

Ala Leu Glu Leu Asn Gln Arg Asp Ala Ala Ala Glu Thr Glu Leu Arg  
 625 630 635 640

Val His Pro Pro Cys Gln Arg His Cys Pro Glu Pro Pro Ser Ala Pro  
 645 650 655

Glu Glu Asn Lys Ala Thr Ser Lys Ala Pro Gln Gly Ser Asn Ser Lys  
 660 665 670

Thr Pro Ile Phe Ser Pro Phe Pro Ser Val Lys Pro Leu Arg Lys Ser  
 675 680 685

Ala Thr Ala Arg Asn Leu Gly Leu Tyr Gly Pro Thr Glu Arg Thr Pro  
 690 695 700

Thr Val His Phe Pro Gln Met Ser Arg Ser Phe Ser Lys Pro Gly Gly  
 705 710 715 720

Gly Asn Ser Gly Thr Lys Lys Arg  
 725

<210> 239  
 <211> 787  
 <212> PRT  
 <213> Homo sapiens

<400> 239

Asp Leu Tyr Leu Leu Leu Ser Tyr Ser Asp Lys Lys Asp His Leu  
 1 5 10 15

Thr Val Glu Glu Leu Ala Gln Phe Leu Lys Val Glu Gln Lys Met Asn  
 20 25 30

Asn Val Thr Thr Asp Tyr Cys Leu Asp Ile Ile Lys Lys Phe Glu Val  
 35 40 45

Ser Glu Glu Asn Lys Val Lys Asn Val Leu Gly Ile Glu Gly Phe Thr  
 50 55 60

Asn Phe Met Arg Ser Pro Ala Cys Asp Ile Phe Asn Pro Leu His His  
 65 70 75 80

Glu Val Tyr Gln Asp Met Asp Gln Pro Leu Cys Asn Tyr Tyr Ile Ala  
 85 90 95

Ser Ser His Asn Thr Tyr Leu Thr Gly Asp Gln Leu Leu Ser Gln Ser  
 100 105 110

Lys Val Asp Met Tyr Ala Arg Val Leu Gln Glu Gly Cys Arg Cys Val  
 115 120 125



Glu Val Asp Cys Trp Asp Gly Pro Asp Gly Glu Pro Val Val His His  
 130 135 140

Gly Tyr Thr Leu Thr Ser Lys Ile Leu Phe Arg Asp Val Val Glu Thr  
 145 150 155 160

Ile Asn Lys His Ala Phe Val Lys Asn Glu Phe Pro Val Ile Leu Ser  
 165 170 175

Ile Glu Asn His Cys Ser Ile Gln Gln Gln Arg Lys Ile Ala Gln Tyr  
 180 185 190

Leu Lys Gly Ile Phe Gly Asp Lys Leu Asp Leu Ser Ser Val Asp Thr  
 195 200 205

Gly Glu Cys Lys Gln Leu Pro Ser Pro Gln Ser Leu Lys Gly Lys Ile  
 210 215 220

Leu Val Lys Gly Lys Lys Leu Pro Tyr His Leu Gly Asp Asp Ala Glu  
 225 230 235 240

Glu Gly Glu Val Ser Asp Glu Asp Ser Ala Asp Glu Ile Glu Asp Glu  
 245 250 255

Cys Lys Phe Lys Leu His Tyr Ser Asn Gly Thr Thr Glu His Gln Val  
 260 265 270

Glu Ser Phe Ile Arg Lys Lys Leu Glu Ser Leu Leu Lys Glu Ser Gln  
 275 280 285

Ile Arg Asp Lys Glu Asp Pro Asp Ser Phe Thr Val Arg Ala Leu Leu  
 290 295 300

Lys Ala Thr His Glu Gly Leu Asn Ala His Leu Lys Gln Ser Pro Asp  
 305 310 315 320

Val Lys Glu Ser Gly Lys Lys Ser His Gly Arg Ser Leu Met Thr Asn  
 325 330 335

Phe Gly Lys His Lys Lys Thr Thr Lys Ser Arg Ser Lys Ser Tyr Ser  
 340 345 350

Thr Asp Asp Glu Glu Asp Thr Gln Gln Ser Thr Gly Lys Glu Gly Gly  
 355 360 365

Gln Leu Tyr Arg Leu Gly Arg Arg Arg Lys Thr Met Lys Leu Cys Arg  
 370 375 380

Glu Leu Ser Asp Leu Val Val Tyr Thr Asn Ser Val Ala Ala Gln Asp  
 385 390 395 400

Ile Val Asp Asp Gly Thr Thr Gly Asn Val Leu Ser Phe Ser Glu Thr  
 405 410 415

Arg Ala His Gln Val Val Gln Gln Lys Ser Glu Gln Phe Met Ile Tyr  
 420 425 430

Asn Gln Lys Gln Leu Thr Arg Ile Tyr Pro Ser Ala Tyr Arg Ile Asp  
 435 440 445

Ser Ser Asn Phe Asn Pro Leu Pro Tyr Trp Asn Ala Gly Cys Gln Leu  
 450 455 460

Val Ala Leu Asn Tyr Gln Ser Glu Gly Arg Met Met Gln Leu Asn Arg  
 465 470 475 480

Ala Lys Phe Lys Ala Asn Gly Asn Cys Gly Tyr Val Leu Lys Pro Gln  
 485 490 495

Gln Met Cys Lys Gly Thr Phe Asn Pro Phe Ser Gly Asp Pro Leu Pro  
 500 505 510

Ala Asn Pro Lys Lys Gln Leu Ile Leu Lys Val Ile Ser Gly Gln Gln  
 515 520 525

Leu Pro Lys Pro Pro Asp Ser Met Phe Gly Asp Arg Gly Glu Ile Ile  
 530 535 540

Asp Pro Phe Val Glu Val Glu Ile Ile Gly Leu Pro Val Asp Cys Cys  
 545 550 555 560

Lys Asp Gln Thr Arg Val Val Asp Asp Asn Gly Phe Asn Pro Val Trp  
 565 570 575

Glu Glu Thr Leu Thr Phe Thr Val His Met Pro Glu Ile Ala Leu Val  
 580 585 590

Arg Phe Leu Val Trp Asp His Asp Pro Ile Gly Arg Asp Phe Val Gly  
 595 600 605

Gln Arg Thr Val Thr Phe Ser Ser Leu Val Pro Gly Tyr Arg His Val  
 610 615 620

Tyr Leu Glu Gly Leu Thr Glu Ala Ser Ile Phe Val His Ile Thr Ile  
 625 630 635 640

Asn Glu Ile Tyr Gly Lys Trp Ser Pro Leu Ile Leu Asn Pro Ser Tyr  
 645 650 655

Thr Ile Leu His Phe Leu Gly Ala Thr Lys Asn Arg Gln Leu Gln Gly  
 660 665 670

Leu Lys Gly Leu Phe Asn Lys Asn Pro Arg His Ser Ser Ser Glu Asn  
 675 680 685

Asn Ser His Tyr Val Arg Lys Arg Ser Ile Gly Asp Arg Ile Leu Arg  
 690 695 700

Arg Thr Ala Ser Ala Pro Ala Lys Gly Arg Lys Lys Ser Lys Met Gly  
 705 710 715 720

Phe Gln Glu Met Val Glu Ile Lys Asp Ser Val Ser Glu Ala Thr Arg  
 725 730 735

Asp Gln Asp Gly Val Leu Arg Arg Thr Thr Arg Ser Leu Gln Ala Arg  
 740 745 750

Pro Val Ser Met Pro Val Asp Arg Asn Leu Leu Gly Ala Leu Ser Leu  
 755 760 765

Pro Val Ser Glu Thr Ala Lys Asp Ile Glu Gly Lys Glu Asn Ser Leu  
 770 775 780

Val Gln Ile  
 785

<210> 240

<211> 665  
 <212> PRT  
 <213> Homo sapiens

<400> 240

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Met Ala His Glu Met Ile Gly Thr Gln Ile Val Thr Glu Arg Leu Val
1           5           10           15

Ala Leu Leu Glu Ser Gly Thr Glu Lys Val Leu Leu Ile Asp Ser Arg
          20           25           30

Pro Phe Val Glu Tyr Asn Thr Ser His Ile Leu Glu Ala Ile Asn Ile
          35           40           45

Asn Cys Ser Lys Leu Met Lys Arg Arg Leu Gln Gln Asp Lys Val Leu
          50           55           60

Ile Thr Glu Leu Ile Gln His Ser Ala Lys His Lys Val Asp Ile Asp
65           70           75           80

Cys Ser Gln Lys Val Val Val Tyr Asp Gln Ser Ser Gln Asp Val Ala
          85           90           95

Ser Leu Ser Ser Asp Cys Phe Leu Thr Val Leu Leu Gly Lys Leu Glu
          100          105          110

Lys Ser Phe Asn Ser Val His Leu Leu Ala Gly Gly Phe Ala Glu Phe
          115          120          125

Ser Arg Cys Phe Pro Gly Leu Cys Glu Gly Lys Ser Thr Leu Val Pro
          130          135          140

Thr Cys Ile Ser Gln Pro Cys Leu Pro Val Ala Asn Ile Gly Pro Thr
145           150           155           160

Arg Ile Leu Pro Asn Leu Tyr Leu Gly Cys Gln Arg Asp Val Leu Asn
          165          170          175

Lys Glu Leu Met Gln Gln Asn Gly Ile Gly Tyr Val Leu Asn Ala Ser
          180          185          190

Asn Thr Cys Pro Lys Pro Asp Phe Ile Pro Glu Ser His Phe Leu Arg
          195          200          205

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Val Pro Val Asn Asp Ser Phe Cys Glu Lys Ile Leu Pro Trp Leu Asp  
 210 215 220

Lys Ser Val Asp Phe Ile Glu Lys Ala Lys Ala Ser Asn Gly Cys Val  
 225 230 235 240

Leu Val His Cys Leu Ala Gly Ile Ser Arg Ser Ala Thr Ile Ala Ile  
 245 250 255

Ala Tyr Ile Met Lys Arg Met Asp Met Ser Leu Asp Glu Ala Tyr Arg  
 260 265 270

Phe Val Lys Glu Lys Arg Pro Thr Ile Ser Pro Asn Phe Asn Phe Leu  
 275 280 285

Gly Gln Leu Leu Asp Tyr Glu Lys Lys Ile Lys Asn Gln Thr Gly Ala  
 290 295 300

Ser Gly Pro Lys Ser Lys Leu Lys Leu Leu His Leu Glu Lys Pro Asn  
 305 310 315 320

Glu Pro Val Pro Ala Val Ser Glu Gly Gly Gln Lys Ser Glu Thr Pro  
 325 330 335

Leu Ser Pro Pro Cys Ala Asp Ser Ala Thr Ser Glu Ala Ala Gly Gln  
 340 345 350

Arg Pro Val His Pro Ala Ser Val Pro Ser Val Pro Ser Val Gln Pro  
 355 360 365

Ser Leu Leu Glu Asp Ser Pro Leu Val Gln Ala Leu Ser Gly Leu His  
 370 375 380

Leu Ser Ala Asp Arg Leu Glu Asp Ser Asn Lys Leu Lys Arg Ser Phe  
 385 390 395 400

Ser Leu Asp Ile Lys Ser Val Ser Tyr Ser Ala Ser Met Ala Ala Ser  
 405 410 415

Leu His Gly Phe Ser Ser Ser Glu Asp Ala Leu Glu Tyr Tyr Lys Pro  
 420 425 430

Ser Thr Thr Leu Asp Gly Thr Asn Lys Leu Cys Gln Phe Ser Pro Val  
 435 440 445

Gln Glu Leu Ser Glu Gln Thr Pro Glu Thr Ser Pro Asp Lys Glu Glu  
 450 455 460

Ala Ser Ile Pro Lys Lys Leu Gln Thr Ala Arg Pro Ser Asp Ser Gln  
 465 470 475 480

Ser Lys Arg Leu His Ser Val Arg Thr Ser Ser Ser Gly Thr Ala Gln  
 485 490 495

Arg Ser Leu Leu Ser Pro Leu His Arg Ser Gly Ser Val Glu Asp Asn  
 500 505 510

Tyr His Thr Ser Phe Leu Phe Gly Leu Ser Thr Ser Gln Gln His Leu  
 515 520 525

Thr Lys Ser Ala Gly Leu Gly Leu Lys Gly Trp His Ser Asp Ile Leu  
 530 535 540

Ala Pro Gln Thr Ser Thr Pro Ser Leu Thr Ser Ser Trp Tyr Phe Ala  
 545 550 555 560

Thr Glu Ser Ser His Phe Tyr Ser Ala Ser Ala Ile Tyr Gly Gly Ser  
 565 570 575

Ala Ser Tyr Ser Ala Tyr Ser Cys Ser Gln Leu Pro Thr Cys Gly Asp  
 580 585 590

Gln Val Tyr Ser Val Arg Arg Arg Gln Lys Pro Ser Asp Arg Ala Asp  
 595 600 605

Ser Arg Arg Ser Trp His Glu Glu Ser Pro Phe Glu Lys Gln Phe Lys  
 610 615 620

Arg Arg Ser Cys Gln Met Glu Phe Gly Glu Ser Ile Met Ser Glu Asn  
 625 630 635 640

Arg Ser Arg Glu Glu Leu Gly Lys Val Gly Ser Gln Ser Ser Phe Ser  
 645 650 655

Gly Ser Met Glu Ile Ile Glu Val Ser

660

665

<210> 241  
 <211> 563  
 <212> PRT  
 <213> Homo sapiens

<400> 241

Met Trp Ala Val Leu Arg Leu Ala Leu Arg Pro Cys Ala Arg Ala Ser  
 1 5 10 15

Pro Ala Gly Pro Arg Ala Tyr His Gly Asp Ser Val Ala Ser Leu Gly  
 20 25 30

Thr Gln Pro Asp Leu Gly Ser Ala Leu Tyr Gln Glu Asn Tyr Lys Gln  
 35 40 45

Met Lys Ala Leu Val Asn Gln Leu His Glu Arg Val Glu His Ile Lys  
 50 55 60

Leu Gly Gly Gly Glu Lys Ala Arg Ala Leu His Ile Ser Arg Gly Lys  
 65 70 75 80

Leu Leu Pro Arg Glu Arg Ile Asp Asn Leu Ile Asp Pro Gly Ser Pro  
 85 90 95

Phe Leu Glu Leu Ser Gln Phe Ala Gly Tyr Gln Leu Tyr Asp Asn Glu  
 100 105 110

Glu Val Pro Gly Gly Gly Ile Ile Thr Gly Ile Gly Arg Val Ser Gly  
 115 120 125

Val Glu Cys Met Ile Ile Ala Asn Asp Ala Thr Val Lys Gly Gly Ala  
 130 135 140

Tyr Tyr Pro Val Thr Val Lys Lys Gln Leu Arg Ala Gln Glu Ile Ala  
 145 150 155 160

Met Gln Asn Arg Leu Pro Cys Ile Tyr Leu Val Asp Ser Gly Gly Ala  
 165 170 175

Tyr Leu Pro Arg Gln Ala Asp Val Phe Pro Asp Arg Asp His Phe Gly  
 180 185 190

Arg Thr Phe Tyr Asn Gln Ala Ile Met Ser Ser Lys Asn Ile Ala Gln  
 195 200 205

Ile Ala Val Val Met Gly Ser Cys Thr Ala Gly Gly Ala Tyr Val Pro  
 210 215 220

Ala Met Ala Asp Glu Asn Ile Ile Val Arg Lys Gln Gly Thr Ile Phe  
 225 230 235 240

Leu Ala Gly Pro Pro Leu Val Lys Ala Ala Thr Gly Glu Glu Val Ser  
 245 250 255

Ala Glu Asp Leu Gly Gly Ala Asp Leu His Cys Arg Lys Ser Gly Val  
 260 265 270

Ser Asp His Trp Ala Leu Asp Asp His His Ala Leu His Leu Thr Arg  
 275 280 285

Lys Val Val Arg Asn Leu Asn Tyr Gln Lys Lys Leu Asp Val Thr Ile  
 290 295 300

Glu Pro Ser Glu Glu Pro Leu Phe Pro Ala Asp Glu Leu Tyr Gly Ile  
 305 310 315 320

Val Gly Ala Asn Leu Lys Arg Ser Phe Asp Val Arg Glu Val Ile Ala  
 325 330 335

Arg Ile Val Asp Gly Ser Arg Phe Thr Glu Phe Lys Ala Phe Tyr Gly  
 340 345 350

Asp Thr Leu Val Thr Gly Phe Ala Arg Ile Phe Gly Tyr Pro Val Gly  
 355 360 365

Ile Val Gly Asn Asn Gly Val Leu Phe Ser Glu Ser Ala Lys Lys Gly  
 370 375 380

Thr His Phe Val Gln Leu Cys Cys Gln Arg Asn Ile Pro Leu Leu Phe  
 385 390 395 400

Leu Gln Asn Ile Thr Gly Phe Met Val Gly Arg Glu Tyr Glu Ala Glu  
 405 410 415



Gly Ile Ala Lys Asp Gly Ala Lys Met Val Ala Ala Val Ala Cys Ala  
 420 425 430

Gln Val Pro Lys Ile Thr Leu Ile Ile Gly Gly Ser Tyr Gly Ala Gly  
 435 440 445

Asn Tyr Gly Met Cys Gly Arg Ala Tyr Ser Pro Arg Phe Leu Tyr Ile  
 450 455 460

Trp Pro Asn Ala Arg Ile Ser Val Met Gly Gly Glu Gln Ala Ala Asn  
 465 470 475 480

Val Leu Ala Thr Ile Thr Lys Asp Gln Arg Ala Arg Glu Gly Lys Gln  
 485 490 495

Phe Ser Ser Ala Asp Glu Ala Ala Leu Lys Glu Pro Ile Ile Lys Lys  
 500 505 510

Phe Glu Glu Glu Gly Asn Pro Tyr Tyr Ser Ser Ala Arg Val Trp Asp  
 515 520 525

Asp Gly Ile Ile Asp Pro Ala Asp Thr Arg Leu Val Leu Gly Leu Ser  
 530 535 540

Phe Ser Ala Ala Leu Asn Ala Pro Ile Glu Lys Thr Asp Phe Gly Ile  
 545 550 555 560

Phe Arg Met

<210> 242  
 <211> 758  
 <212> PRT  
 <213> Homo sapiens

<400> 242

Met Ala Glu Pro Arg Gln Glu Phe Glu Val Met Glu Asp His Ala Gly  
 1 5 10 15

Thr Tyr Gly Leu Gly Asp Arg Lys Asp Gln Gly Gly Tyr Thr Met His  
 20 25 30

Gln Asp Gln Glu Gly Asp Thr Asp Ala Gly Leu Lys Glu Ser Pro Leu  
 35 40 45

Gln Thr Pro Thr Glu Asp Gly Ser Glu Glu Pro Gly Ser Glu Thr Ser  
 50 55 60

Asp Ala Lys Ser Thr Pro Thr Ala Glu Asp Val Thr Ala Pro Leu Val  
 65 70 75 80

Asp Glu Gly Ala Pro Gly Lys Gln Ala Ala Ala Gln Pro His Thr Glu  
 85 90 95

Ile Pro Glu Gly Thr Thr Ala Glu Glu Ala Gly Ile Gly Asp Thr Pro  
 100 105 110

Ser Leu Glu Asp Glu Ala Ala Gly His Val Thr Gln Glu Pro Glu Ser  
 115 120 125

Gly Lys Val Val Gln Glu Gly Phe Leu Arg Glu Pro Gly Pro Pro Gly  
 130 135 140

Leu Ser His Gln Leu Met Ser Gly Met Pro Gly Ala Pro Leu Leu Pro  
 145 150 155 160

Glu Gly Pro Arg Glu Ala Thr Arg Gln Pro Ser Gly Thr Gly Pro Glu  
 165 170 175

Asp Thr Glu Gly Gly Arg His Ala Pro Glu Leu Leu Lys His Gln Leu  
 180 185 190

Leu Gly Asp Leu His Gln Glu Gly Pro Pro Leu Lys Gly Ala Gly Gly  
 195 200 205

Lys Glu Arg Pro Gly Ser Lys Glu Glu Val Asp Glu Asp Arg Asp Val  
 210 215 220

Asp Glu Ser Ser Pro Gln Asp Ser Pro Pro Ser Lys Ala Ser Pro Ala  
 225 230 235 240

Gln Asp Gly Arg Pro Pro Gln Thr Ala Ala Arg Glu Ala Thr Ser Ile  
 245 250 255

Pro Gly Phe Pro Ala Glu Gly Ala Ile Pro Leu Pro Val Asp Phe Leu  
 260 265 270

Ser Lys Val Ser Thr Glu Ile Pro Ala Ser Glu Pro Asp Gly Pro Ser  
 275 280 285

Val Gly Arg Ala Lys Gly Gln Asp Ala Pro Leu Glu Phe Thr Phe His  
 290 295 300

Val Glu Ile Thr Pro Asn Val Gln Lys Glu Gln Ala His Ser Glu Glu  
 305 310 315 320

His Leu Gly Arg Ala Ala Phe Pro Gly Ala Pro Gly Glu Gly Pro Glu  
 325 330 335

Ala Arg Gly Pro Ser Leu Gly Glu Asp Thr Lys Glu Ala Asp Leu Pro  
 340 345 350

Glu Pro Ser Glu Lys Gln Pro Ala Ala Ala Pro Arg Gly Lys Pro Val  
 355 360 365

Ser Arg Val Pro Gln Leu Lys Ala Arg Met Val Ser Lys Ser Lys Asp  
 370 375 380

Gly Thr Gly Ser Asp Asp Lys Lys Ala Lys Thr Ser Thr Arg Ser Ser  
 385 390 395 400

Ala Lys Thr Leu Lys Asn Arg Pro Cys Leu Ser Pro Lys Leu Pro Thr  
 405 410 415

Pro Gly Ser Ser Asp Pro Leu Ile Gln Pro Ser Ser Pro Ala Val Cys  
 420 425 430

Pro Glu Pro Pro Ser Ser Pro Lys His Val Ser Ser Val Thr Ser Arg  
 435 440 445

Thr Gly Ser Ser Gly Ala Lys Glu Met Lys Leu Lys Gly Ala Asp Gly  
 450 455 460

Lys Thr Lys Ile Ala Thr Pro Arg Gly Ala Ala Pro Pro Gly Gln Lys  
 465 470 475 480

Gly Gln Ala Asn Ala Thr Arg Ile Pro Ala Lys Thr Pro Pro Ala Pro  
 485 490 495

Lys Thr Pro Pro Ser Ser Gly Glu Pro Pro Lys Ser Gly Asp Arg Ser  
                   500                  505                  510

Gly Tyr Ser Ser Pro Gly Ser Pro Gly Thr Pro Gly Ser Arg Ser Arg  
                   515                  520                  525

Thr Pro Ser Leu Pro Thr Pro Pro Thr Arg Glu Pro Lys Lys Val Ala  
                   530                  535                  540

Val Val Arg Thr Pro Pro Lys Ser Pro Ser Ser Ala Lys Ser Arg Leu  
                   545                  550                  555                  560

Gln Thr Ala Pro Val Pro Met Pro Asp Leu Lys Asn Val Lys Ser Lys  
                   565                  570                  575

Ile Gly Ser Thr Glu Asn Leu Lys His Gln Pro Gly Gly Gly Lys Val  
                   580                  585                  590

Gln Ile Ile Asn Lys Lys Leu Asp Leu Ser Asn Val Gln Ser Lys Cys  
                   595                  600                  605

Gly Ser Lys Asp Asn Ile Lys His Val Pro Gly Gly Gly Ser Val Gln  
                   610                  615                  620

Ile Val Tyr Lys Pro Val Asp Leu Ser Lys Val Thr Ser Lys Cys Gly  
                   625                  630                  635                  640

Ser Leu Gly Asn Ile His His Lys Pro Gly Gly Gly Gln Val Glu Val  
                   645                  650                  655

Lys Ser Glu Lys Leu Asp Phe Lys Asp Arg Val Gln Ser Lys Ile Gly  
                   660                  665                  670

Ser Leu Asp Asn Ile Thr His Val Pro Gly Gly Gly Asn Lys Lys Ile  
                   675                  680                  685

Glu Thr His Lys Leu Thr Phe Arg Glu Asn Ala Lys Ala Lys Thr Asp  
                   690                  695                  700

His Gly Ala Glu Ile Val Tyr Lys Ser Pro Val Val Ser Gly Asp Thr  
                   705                  710                  715                  720

Ser Pro Arg His Leu Ser Asn Val Ser Ser Thr Gly Ser Ile Asp Met

725

730

735

Val Asp Ser Pro Gln Leu Ala Thr Leu Ala Asp Glu Val Ser Ala Ser  
 740 745 750

Leu Ala Lys Gln Gly Leu  
 755

<210> 243  
 <211> 547  
 <212> PRT  
 <213> Homo sapiens

<400> 243

Met Glu Asn Asp Glu Ser Ala Lys Glu Glu Lys Ser Asp Leu Lys Glu  
 1 5 10 15

Lys Ser Thr Gly Ser Lys Lys Ala Asn Arg Phe His Pro Tyr Ser Lys  
 20 25 30

Asp Lys Asn Ser Gly Thr Gly Glu Lys Lys Gly Pro Asn Arg Asn Arg  
 35 40 45

Val Phe Ile Ser Asn Ile Pro Tyr Asp Met Lys Trp Gln Ala Ile Lys  
 50 55 60

Asp Leu Met Arg Glu Lys Val Gly Glu Val Thr Tyr Val Glu Leu Phe  
 65 70 75 80

Lys Asp Ala Glu Gly Lys Ser Arg Gly Cys Gly Val Val Glu Phe Lys  
 85 90 95

Asp Glu Glu Phe Val Lys Lys Ala Leu Glu Thr Met Asn Lys Tyr Asp  
 100 105 110

Leu Ser Gly Arg Arg Val Asn Ile Lys Glu Asp Pro Asp Gly Glu Asn  
 115 120 125

Ala Arg Arg Ala Leu Gln Arg Thr Gly Thr Ser Phe Gln Gly Ser His  
 130 135 140

Ala Ser Asp Val Gly Ser Gly Leu Val Asn Leu Pro Pro Ser Ile Leu  
 145 150 155 160

Asn Asn Pro Asn Ile Pro Pro Glu Val Ile Ser Asn Leu Gln Ala Gly  
 165 170 175

Arg Leu Gly Ser Thr Ile Phe Val Ala Asn Leu Asp Phe Lys Val Gly  
 180 185 190

Trp Lys Lys Leu Lys Glu Val Phe Ser Ile Ala Gly Thr Val Lys Ala  
 195 200 205

Gly Ser Tyr Lys Glu Asp Lys Asp Gly Lys Ser Arg Gly Met Gly Thr  
 210 215 220

Val Thr Phe Glu Gln Ala Ile Glu Ala Val Gln Ala Ile Ser Met Phe  
 225 230 235 240

Asn Gly Gln Phe Leu Phe Asp Arg Pro Met His Val Lys Met Asp Asp  
 245 250 255

Lys Ser Val Pro His Glu Glu Tyr Arg Ser Pro Asp Gly Lys Thr Pro  
 260 265 270

Gln Leu Pro Arg Gly Leu Gly Gly Ile Gly Met Gly Leu Gly Pro Gly  
 275 280 285

Gly Gln Pro Ile Ser Ala Ser Gln Leu Asn Ile Gly Gly Val Met Gly  
 290 295 300

Asn Leu Gly Pro Gly Gly Met Gly Met Asp Gly Pro Gly Phe Gly Gly  
 305 310 315 320

Met Asn Arg Ile Gly Gly Gly Ile Gly Phe Gly Gly Leu Glu Ala Met  
 325 330 335

Asn Ser Met Gly Gly Phe Gly Gly Val Gly Arg Met Gly Glu Leu Tyr  
 340 345 350

Arg Gly Ala Met Thr Ser Ser Met Glu Arg Asp Phe Gly His Arg Asp  
 355 360 365

Ile Gly Leu Ser Arg Gly Phe Gly Asp Ser Phe Gly Arg Leu Gly Ser  
 370 375 380

Ala Met Ile Gly Gly Ile Thr Gly Arg Ile Gly Ser Ser Asn Met Gly  
385 390 395 400

Pro Val Gly Ser Gly Ile Ser Gly Gly Met Gly Ser Met Asn Ser Val  
405 410 415

Thr Gly Gly Met Gly Met Gly Leu Asp Arg Met Ser Ser Ser Phe Asp  
420 425 430

Arg Met Gly Pro Gly Ile Gly Ala Ile Leu Glu Arg Ser Ile Asp Met  
435 440 445

Asp Arg Gly Phe Leu Ser Gly Pro Met Gly Ser Gly Met Arg Glu Arg  
450 455 460

Ile Gly Ser Lys Gly Asn Gln Ile Phe Val Arg Asn Leu Pro Phe Asp  
465 470 475 480

Leu Thr Trp Gln Lys Leu Lys Glu Lys Phe Ser Gln Cys Gly His Val  
485 490 495

Met Phe Ala Glu Ile Lys Met Glu Asn Gly Lys Ser Lys Gly Cys Gly  
500 505 510

Thr Val Arg Phe Asp Ser Pro Glu Ser Ala Glu Lys Ala Cys Arg Ile  
515 520 525

Met Asn Gly Ile Lys Ile Ser Gly Arg Glu Ile Asp Val Arg Leu Asp  
530 535 540

Arg Asn Ala  
545

<210> 244  
<211> 1022  
<212> PRT  
<213> Homo sapiens

<400> 244

Met Asn Asn Asn Trp Asn Val Cys Phe Phe Leu Phe Cys Pro Ser Ile  
1 5 10 15

Thr Arg Thr Phe Ala Ser Gly Lys Thr Glu Lys Val Ile Phe Gln Ala  
20 25 30

Leu Lys Glu Leu Gly Leu Pro Ser Gly Lys Asn Asp Glu Ile Glu Pro  
 35 40 45

Thr Ala Phe Ser Tyr Glu Lys Phe Tyr Glu Leu Thr Gln Lys Ile Cys  
 50 55 60

Pro Arg Thr Asp Ile Glu Asp Leu Phe Lys Lys Ile Asn Gly Asp Lys  
 65 70 75 80

Thr Asp Tyr Leu Thr Val Asp Gln Leu Val Ser Phe Leu Asn Glu His  
 85 90 95

Gln Arg Asp Pro Arg Leu Asn Glu Ile Leu Phe Pro Phe Tyr Asp Ala  
 100 105 110

Lys Arg Ala Met Gln Ile Ile Glu Met Tyr Glu Pro Asp Glu Asp Leu  
 115 120 125

Lys Lys Lys Gly Leu Ile Ser Ser Asp Gly Phe Cys Arg Tyr Leu Met  
 130 135 140

Ser Asp Glu Asn Ala Pro Val Phe Leu Asp Arg Leu Glu Leu Tyr Gln  
 145 150 155 160

Glu Met Asp His Pro Leu Ala His Tyr Phe Ile Ser Ser Ser His Asn  
 165 170 175

Thr Tyr Leu Thr Gly Arg Gln Phe Gly Gly Lys Ser Ser Val Glu Met  
 180 185 190

Tyr Arg Gln Val Leu Leu Ala Gly Cys Arg Cys Val Glu Leu Asp Cys  
 195 200 205

Trp Asp Gly Lys Gly Glu Asp Gln Glu Pro Ile Ile Thr His Gly Lys  
 210 215 220

Ala Met Cys Thr Asp Ile Leu Phe Lys Asp Val Ile Gln Ala Ile Lys  
 225 230 235 240

Glu Thr Ala Phe Val Thr Ser Glu Tyr Pro Val Ile Leu Ser Phe Glu  
 245 250 255



Asn His Cys Ser Lys Tyr Gln Gln Tyr Lys Met Ser Lys Tyr Cys Glu  
 260 265 270

Asp Leu Phe Gly Asp Leu Leu Leu Lys Gln Ala Leu Glu Ser His Pro  
 275 280 285

Leu Glu Pro Gly Arg Pro Leu Pro Ser Pro Asn Asp Leu Lys Arg Lys  
 290 295 300

Ile Leu Ile Lys Asn Lys Arg Leu Lys Pro Glu Val Glu Lys Lys Gln  
 305 310 315 320

Leu Glu Ala Leu Arg Ser Met Met Glu Ala Gly Glu Ser Ala Ser Pro  
 325 330 335

Ala Asn Ile Leu Glu Asp Asp Asn Glu Glu Glu Ile Glu Ser Ala Asp  
 340 345 350

Gln Glu Glu Glu Ala His Pro Glu Phe Lys Phe Gly Asn Glu Leu Ser  
 355 360 365

Ala Asp Asp Leu Gly His Lys Glu Ala Val Ala Asn Ser Val Lys Lys  
 370 375 380

Gly Leu Val Thr Val Glu Asp Glu Gln Ala Trp Met Ala Ser Tyr Lys  
 385 390 395 400

Tyr Val Gly Ala Thr Thr Asn Ile His Pro Tyr Leu Ser Thr Met Ile  
 405 410 415

Asn Tyr Ala Gln Pro Val Lys Phe Gln Gly Phe His Val Ala Glu Glu  
 420 425 430

Arg Asn Ile His Tyr Asn Met Ser Ser Phe Asn Glu Ser Val Gly Leu  
 435 440 445

Gly Tyr Leu Lys Thr His Ala Ile Glu Phe Val Asn Tyr Asn Lys Arg  
 450 455 460

Gln Met Ser Arg Ile Tyr Pro Lys Gly Gly Arg Val Asp Ser Ser Asn  
 465 470 475 480

Tyr Met Pro Gln Ile Phe Trp Asn Ala Gly Cys Gln Met Val Ser Leu  
 485 490 495

Asn Tyr Gln Thr Pro Asp Leu Ala Met Gln Leu Asn Gln Gly Lys Phe  
 500 505 510

Glu Tyr Asn Gly Ser Cys Gly Tyr Leu Leu Lys Pro Asp Phe Met Arg  
 515 520 525

Arg Pro Asp Arg Thr Phe Asp Pro Phe Ser Glu Thr Pro Val Asp Gly  
 530 535 540

Val Ile Ala Ala Thr Cys Ser Val Gln Val Ile Ser Gly Gln Phe Leu  
 545 550 555 560

Ser Asp Lys Lys Ile Gly Thr Tyr Val Glu Val Asp Met Tyr Gly Leu  
 565 570 575

Pro Thr Asp Thr Ile Arg Lys Glu Phe Arg Thr Arg Met Val Met Asn  
 580 585 590

Asn Gly Leu Asn Pro Val Tyr Asn Glu Glu Ser Leu Val Phe Arg Lys  
 595 600 605

Val Ile Leu Pro Asp Leu Ala Val Leu Arg Ile Ala Val Tyr Asp Asp  
 610 615 620

Asn Asn Lys Leu Ile Gly Gln Arg Ile Pro Pro Leu Asp Gly Leu Gln  
 625 630 635 640

Ala Gly Tyr Arg His Ile Ser Leu Arg Asn Glu Gly Asn Lys Pro Leu  
 645 650 655

Ser Leu Pro Thr Ile Phe Cys Asn Ile Val Leu Lys Thr Tyr Val Pro  
 660 665 670

Asp Gly Phe Gly Asp Ile Val Asp Ala Leu Ser Asp Pro Lys Thr Phe  
 675 680 685

Leu Ser Ile Thr Glu Lys Arg Ala Asp Gln Met Arg Ala Met Gly Ile  
 690 695 700

Glu Thr Ser Asp Ile Ala Asp Val Pro Ser Asp Thr Ser Lys Asn Asp

705	710	715	720
Lys Lys Gly Lys Ala Asn Thr Ala Lys Ala Asn Val Thr Pro Gln Ser	725	730	735
Ser Ser Glu Leu Arg Pro Thr Thr Thr Ala Ala Leu Pro Ser Gly Val	740	745	750
Glu Ala Lys Lys Gly Ile Glu Leu Ile Pro Gln Val Arg Ile Glu Asp	755	760	765
Leu Lys Gln Met Lys Ala Tyr Leu Lys His Leu Lys Lys Gln Gln Lys	770	775	780
Glu Leu Asn Ser Leu Lys Lys Lys His Ala Lys Glu His Ser Thr Met	785	790	795
Gln Lys Leu His Cys Thr Gln Val Asp Lys Ile Val Ala Gln Tyr Asp	805	810	815
Lys Glu Lys Ser Thr His Glu Lys Ile Leu Glu Lys Ala Met Lys Lys	820	825	830
Lys Gly Gly Ser Asn Cys Leu Glu Met Lys Lys Glu Thr Glu Ile Lys	835	840	845
Ile Gln Thr Leu Thr Ser Asp His Lys Ser Lys Val Lys Glu Ile Val	850	855	860
Ala Gln His Thr Lys Glu Trp Ser Glu Met Ile Asn Thr His Ser Ala	865	870	875
Glu Glu Gln Glu Ile Arg Asp Leu His Leu Ser Gln Gln Cys Glu Leu	885	890	895
Leu Lys Lys Leu Leu Ile Asn Ala His Glu Gln Gln Thr Gln Gln Leu	900	905	910
Lys Leu Ser His Asp Arg Glu Ser Lys Glu Met Arg Ala His Gln Ala	915	920	925
Lys Ile Ser Met Glu Asn Ser Lys Ala Ile Ser Gln Asp Lys Ser Ile	930	935	940

Lys Asn Lys Ala Glu Arg Glu Arg Arg Val Arg Glu Leu Asn Ser Ser  
 945 950 955 960

Asn Thr Lys Lys Phe Leu Glu Glu Arg Lys Arg Leu Ala Met Lys Gln  
 965 970 975

Ser Lys Glu Met Asp Gln Leu Lys Lys Val Gln Leu Glu His Leu Glu  
 980 985 990

Phe Leu Glu Lys Gln Asn Glu Gln Ala Lys Glu Met Gln Gln Met Val  
 995 1000 1005

Lys Leu Glu Ala Glu Met Asp Arg Arg Pro Ala Thr Val Val  
 1010 1015 1020

<210> 245  
 <211> 335  
 <212> PRT  
 <213> Homo sapiens

<400> 245

Met Gly Ser Ala Ser Pro Gly Leu Ser Ser Val Ser Pro Ser His Leu  
 1 5 10 15

Leu Leu Pro Pro Asp Thr Val Ser Arg Thr Gly Leu Glu Lys Ala Ala  
 20 25 30

Ala Gly Ala Val Gly Leu Glu Arg Arg Asp Trp Ser Pro Ser Pro Pro  
 35 40 45

Ala Thr Pro Glu Gln Gly Leu Ser Ala Phe Tyr Leu Ser Tyr Phe Asp  
 50 55 60

Met Leu Tyr Pro Glu Asp Ser Ser Trp Ala Ala Lys Ala Pro Gly Ala  
 65 70 75 80

Ser Ser Arg Glu Glu Pro Pro Glu Glu Pro Glu Gln Cys Pro Val Ile  
 85 90 95

Asp Ser Gln Ala Pro Ala Gly Ser Leu Asp Leu Val Pro Gly Gly Leu  
 100 105 110

Thr Leu Glu Glu His Ser Leu Glu Gln Val Gln Ser Met Val Val Gly  
 115 120 125  
 Glu Val Leu Lys Asp Ile Glu Thr Ala Cys Lys Leu Leu Asn Ile Thr  
 130 135 140  
 Ala Asp Pro Met Asp Trp Ser Pro Ser Asn Val Gln Lys Trp Leu Leu  
 145 150 155 160  
 Trp Thr Glu His Gln Tyr Arg Leu Pro Pro Met Gly Lys Ala Phe Gln  
 165 170 175  
 Glu Leu Ala Gly Lys Glu Leu Cys Ala Met Ser Glu Glu Gln Phe Arg  
 180 185 190  
 Gln Arg Ser Pro Leu Gly Gly Asp Val Leu His Ala His Leu Asp Ile  
 195 200 205  
 Trp Lys Ser Ala Ala Trp Met Lys Glu Arg Thr Ser Pro Gly Ala Ile  
 210 215 220  
 His Tyr Cys Ala Ser Thr Ser Glu Glu Ser Trp Thr Asp Ser Glu Val  
 225 230 235 240  
 Asp Ser Ser Cys Ser Gly Gln Pro Ile His Leu Trp Gln Phe Leu Lys  
 245 250 255  
 Glu Leu Leu Leu Lys Pro His Ser Tyr Gly Arg Phe Ile Arg Trp Leu  
 260 265 270  
 Asn Lys Glu Lys Gly Ile Phe Lys Ile Glu Asp Ser Ala Gln Val Ala  
 275 280 285  
 Arg Leu Trp Gly Ile Arg Lys Asn Arg Pro Ala Met Asn Tyr Asp Lys  
 290 295 300  
 Leu Ser Arg Ser Ile Arg Gln Tyr Tyr Lys Lys Gly Ile Ile Arg Lys  
 305 310 315 320  
 Pro Asp Ile Ser Gln Arg Leu Val Tyr Gln Phe Val His Pro Ile  
 325 330 335  
 <210> 246

<211> 174  
 <212> PRT  
 <213> Homo sapiens

<400> 246

Met Ala Ala Ala Met Val Pro Gly Arg Ser Glu Ser Trp Glu Arg Gly  
 1 5 10 15

Glu Pro Gly Arg Pro Ala Leu Tyr Phe Cys Gly Ser Ile Arg Gly Gly  
 20 25 30

Arg Glu Asp Arg Thr Leu Tyr Glu Arg Ile Val Ser Arg Leu Arg Arg  
 35 40 45

Phe Gly Thr Val Leu Thr Glu His Val Ala Ala Ala Glu Leu Gly Ala  
 50 55 60

Arg Gly Glu Glu Ala Ala Gly Gly Asp Arg Leu Ile His Glu Gln Asp  
 65 70 75 80

Leu Glu Trp Leu Gln Gln Ala Asp Val Val Val Ala Glu Val Thr Gln  
 85 90 95

Pro Ser Leu Gly Val Gly Tyr Glu Leu Gly Arg Ala Val Ala Phe Asn  
 100 105 110

Lys Arg Ile Leu Cys Leu Phe Arg Pro Gln Ser Gly Arg Val Leu Ser  
 115 120 125

Ala Met Ile Arg Gly Ala Ala Asp Gly Ser Arg Phe Gln Val Trp Asp  
 130 135 140

Tyr Glu Glu Gly Glu Val Glu Ala Leu Leu Asp Arg Tyr Phe Glu Ala  
 145 150 155 160

Asp Pro Pro Gly Gln Val Ala Ala Ser Pro Asp Pro Thr Thr  
 165 170

<210> 247  
 <211> 665  
 <212> PRT  
 <213> Homo sapiens  
 <400> 247

Met Ala His Glu Met Ile Gly Thr Gln Ile Val Thr Glu Arg Leu Val  
 1 5 10 15

Ala Leu Leu Glu Ser Gly Thr Glu Lys Val Leu Leu Ile Asp Ser Arg  
 20 25 30

Pro Phe Val Glu Tyr Asn Thr Ser His Ile Leu Glu Ala Ile Asn Ile  
 35 40 45

Asn Cys Ser Lys Leu Met Lys Arg Arg Leu Gln Gln Asp Lys Val Leu  
 50 55 60

Ile Thr Glu Leu Ile Gln His Ser Ala Lys His Lys Val Asp Ile Asp  
 65 70 75 80

Cys Ser Gln Lys Val Val Val Tyr Asp Gln Ser Ser Gln Asp Val Ala  
 85 90 95

Ser Leu Ser Ser Asp Cys Phe Leu Thr Val Leu Leu Gly Lys Leu Glu  
 100 105 110

Lys Ser Phe Asn Ser Val His Leu Leu Ala Gly Gly Phe Ala Glu Phe  
 115 120 125

Ser Arg Cys Phe Pro Gly Leu Cys Glu Gly Lys Ser Thr Leu Val Pro  
 130 135 140

Thr Cys Ile Ser Gln Pro Cys Leu Pro Val Ala Asn Ile Gly Pro Thr  
 145 150 155 160

Arg Ile Leu Pro Asn Leu Tyr Leu Gly Cys Gln Arg Asp Val Leu Asn  
 165 170 175

Lys Glu Leu Met Gln Gln Asn Gly Ile Gly Tyr Val Leu Asn Ala Ser  
 180 185 190

Asn Thr Cys Pro Lys Pro Asp Phe Ile Pro Glu Ser His Phe Leu Arg  
 195 200 205

Val Pro Val Asn Asp Ser Phe Cys Glu Lys Ile Leu Pro Trp Leu Asp  
 210 215 220

Lys Ser Val Asp Phe Ile Glu Lys Ala Lys Ala Ser Asn Gly Cys Val

438



Ala Ser Ile Pro Lys Lys Leu Gln Thr Ala Arg Pro Ser Asp Ser Gln  
465 470 475 480

Ser Lys Arg Leu His Ser Val Arg Thr Ser Ser Ser Gly Thr Ala Gln  
485 490 495

Arg Ser Leu Leu Ser Pro Leu His Arg Ser Gly Ser Val Glu Asp Asn  
500 505 510

Tyr His Thr Ser Phe Leu Phe Gly Leu Ser Thr Ser Gln Gln His Leu  
515 520 525

Thr Lys Ser Ala Gly Leu Gly Leu Lys Gly Trp His Ser Asp Ile Leu  
530 535 540

Ala Pro Gln Thr Ser Thr Pro Ser Leu Thr Ser Ser Trp Tyr Phe Ala  
545 550 555 560

Thr Glu Ser Ser His Phe Tyr Ser Ala Ser Ala Ile Tyr Gly Gly Ser  
565 570 575

Ala Ser Tyr Ser Ala Tyr Ser Cys Ser Gln Leu Pro Thr Cys Gly Asp  
580 585 590

Gln Val Tyr Ser Val Arg Arg Arg Gln Lys Pro Ser Asp Arg Ala Asp  
595 600 605

Ser Arg Arg Ser Trp His Glu Glu Ser Pro Phe Glu Lys Gln Phe Lys  
610 615 620

Arg Arg Ser Cys Gln Met Glu Phe Gly Glu Ser Ile Met Ser Glu Asn  
625 630 635 640

Arg Ser Arg Glu Glu Leu Gly Lys Val Gly Ser Gln Ser Ser Phe Ser  
645 650 655

Gly Ser Met Glu Ile Ile Glu Val Ser  
660 665

<210> 248  
<211> 301  
<212> PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 248

Met Lys Ser Asn Pro Ala Ile Gln Ala Ala Ile Asp Leu Thr Ala Gly  
 1 5 10 15

Ala Ala Gly Gly Thr Ala Cys Val Leu Thr Gly Gln Pro Phe Asp Thr  
 20 25 30

Met Lys Val Lys Met Gln Thr Phe Pro Asp Leu Tyr Arg Gly Leu Thr  
 35 40 45

Asp Cys Cys Leu Lys Thr Tyr Ser Gln Val Gly Phe Arg Gly Phe Tyr  
 50 55 60

Lys Gly Thr Ser Pro Ala Leu Ile Ala Asn Ile Ala Glu Asn Ser Val  
 65 70 75 80

Leu Phe Met Cys Tyr Gly Phe Cys Gln Gln Val Val Arg Lys Val Ala  
 85 90 95

Gly Leu Asp Lys Gln Ala Lys Leu Ser Asp Leu Gln Asn Ala Ala Ala  
 100 105 110

Gly Ser Phe Ala Ser Ala Phe Ala Ala Leu Val Leu Cys Pro Thr Glu  
 115 120 125

Leu Val Lys Cys Arg Leu Gln Thr Met Tyr Glu Met Glu Thr Ser Gly  
 130 135 140

Lys Ile Ala Lys Ser Gln Asn Thr Val Trp Ser Val Ile Lys Ser Ile  
 145 150 155 160

Leu Arg Lys Asp Gly Pro Leu Gly Phe Tyr His Gly Leu Ser Ser Thr  
 165 170 175

Leu Leu Arg Glu Val Pro Gly Tyr Phe Phe Phe Phe Gly Gly Tyr Glu  
 180 185 190

Leu Ser Arg Ser Phe Phe Ala Ser Gly Arg Ser Lys Asp Glu Leu Gly  
 195 200 205

Pro Val Pro Leu Met Leu Ser Gly Gly Val Gly Gly Ile Cys Leu Trp

210                                      215                                      220  
 Leu Ala Val Tyr Pro Val Asp Cys Ile Lys Ser Arg Ile Gln Val Leu  
 225                                      230                                      235                                      240  
 Ser Met Ser Gly Lys Gln Ala Gly Phe Ile Arg Thr Phe Ile Asn Val  
 245                                      250                                      255  
 Val Lys Asn Glu Gly Ile Thr Ala Leu Tyr Ser Gly Leu Lys Pro Thr  
 260                                      265                                      270  
 Met Ile Arg Ala Phe Pro Ala Asn Gly Ala Leu Phe Leu Ala Tyr Glu  
 275                                      280                                      285  
 Tyr Ser Arg Lys Leu Met Met Asn Gln Leu Glu Ala Tyr  
 290                                      295                                      300  
  
 <210> 249  
 <211> 337  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 249  
 Met Ala Ala Pro Arg Asp Asn Val Thr Leu Leu Phe Lys Leu Tyr Cys  
 1                                      5                                      10                                      15  
 Leu Ala Val Met Thr Leu Met Ala Ala Val Tyr Thr Ile Ala Leu Arg  
 20                                      25                                      30  
 Tyr Thr Arg Thr Ser Asp Lys Glu Leu Tyr Phe Ser Thr Thr Ala Val  
 35                                      40                                      45  
 Cys Ile Thr Glu Val Ile Lys Leu Leu Leu Ser Val Gly Ile Leu Ala  
 50                                      55                                      60  
 Lys Glu Thr Gly Ser Leu Gly Arg Phe Lys Ala Ser Leu Arg Glu Asn  
 65                                      70                                      75                                      80  
 Val Leu Gly Ser Pro Lys Glu Leu Leu Lys Leu Ser Val Pro Ser Leu  
 85                                      90                                      95  
 Val Tyr Ala Val Gln Asn Asn Met Ala Phe Leu Ala Leu Ser Asn Leu  
 100                                      105                                      110

Asp Ala Ala Val Tyr Gln Val Thr Tyr Gln Leu Lys Ile Pro Cys Thr  
 115 120 125

Ala Leu Cys Thr Val Leu Met Leu Asn Arg Thr Leu Ser Lys Leu Gln  
 130 135 140

Trp Val Ser Val Phe Met Leu Cys Ala Gly Val Thr Leu Val Gln Trp  
 145 150 155 160

Lys Pro Ala Gln Ala Thr Lys Val Val Val Glu Gln Asn Pro Leu Leu  
 165 170 175

Gly Phe Gly Ala Ile Ala Ile Ala Val Leu Cys Ser Gly Phe Ala Gly  
 180 185 190

Val Tyr Phe Glu Lys Val Leu Lys Ser Ser Asp Thr Ser Leu Trp Val  
 195 200 205

Arg Asn Ile Gln Met Tyr Leu Ser Gly Ile Ile Val Thr Leu Ala Gly  
 210 215 220

Val Tyr Leu Ser Asp Gly Ala Glu Ile Lys Glu Lys Gly Phe Phe Tyr  
 225 230 235 240

Gly Tyr Thr Tyr Tyr Val Trp Phe Val Ile Phe Leu Ala Ser Val Gly  
 245 250 255

Gly Leu Tyr Thr Ser Val Val Val Lys Tyr Thr Asp Asn Ile Met Lys  
 260 265 270

Gly Phe Ser Ala Ala Ala Ala Ile Val Leu Ser Thr Ile Ala Ser Val  
 275 280 285

Met Leu Phe Gly Leu Gln Ile Thr Leu Thr Phe Ala Leu Gly Thr Leu  
 290 295 300

Leu Val Cys Val Ser Ile Tyr Leu Tyr Gly Leu Pro Arg Gln Asp Thr  
 305 310 315 320

Thr Ser Ile Gln Gln Gly Glu Thr Ala Ser Lys Glu Arg Val Ile Gly  
 325 330 335

Val

<210> 250  
 <211> 487  
 <212> PRT  
 <213> Homo sapiens

<400> 250

Met Met His Phe Lys Ser Gly Leu Glu Leu Thr Glu Leu Gln Asn Met  
 1 5 10 15

Thr Val Pro Glu Asp Asp Asn Ile Ser Asn Asp Ser Asn Asp Phe Thr  
 20 25 30

Glu Val Glu Asn Gly Gln Ile Asn Ser Lys Phe Ile Ser Asp Arg Glu  
 35 40 45

Ser Arg Arg Ser Leu Thr Asn Ser His Leu Glu Lys Lys Lys Cys Asp  
 50 55 60

Glu Tyr Ile Pro Gly Thr Thr Ser Leu Gly Met Ser Val Phe Asn Leu  
 65 70 75 80

Ser Asn Ala Ile Met Gly Ser Gly Ile Leu Gly Leu Ala Phe Ala Leu  
 85 90 95

Ala Asn Thr Gly Ile Leu Leu Phe Leu Val Leu Leu Thr Ser Val Thr  
 100 105 110

Leu Leu Ser Ile Tyr Ser Ile Asn Leu Leu Leu Ile Cys Ser Lys Glu  
 115 120 125

Thr Gly Cys Met Val Tyr Glu Lys Leu Gly Glu Gln Val Phe Gly Thr  
 130 135 140

Thr Gly Lys Phe Val Ile Phe Gly Ala Thr Ser Leu Gln Asn Thr Gly  
 145 150 155 160

Ala Met Leu Ser Tyr Leu Phe Ile Val Lys Asn Glu Leu Pro Ser Ala  
 165 170 175

Ile Lys Phe Leu Met Gly Lys Glu Glu Thr Phe Ser Ala Trp Tyr Val  
 180 185 190

Asp Gly Arg Val Leu Val Val Ile Val Thr Phe Gly Ile Ile Leu Pro  
 195 200 205

Leu Cys Leu Leu Lys Asn Leu Gly Tyr Leu Gly Tyr Thr Ser Gly Phe  
 210 215 220

Ser Leu Ser Cys Met Val Phe Phe Leu Ile Val Val Ile Tyr Lys Lys  
 225 230 235 240

Phe Gln Ile Pro Cys Ile Val Pro Glu Leu Asn Ser Thr Ile Ser Ala  
 245 250 255

Asn Ser Thr Asn Ala Asp Thr Cys Thr Pro Lys Tyr Val Thr Phe Asn  
 260 265 270

Ser Lys Thr Val Tyr Ala Leu Pro Thr Ile Ala Phe Ala Phe Val Cys  
 275 280 285

His Pro Ser Val Leu Pro Ile Tyr Ser Glu Leu Lys Asp Arg Ser Gln  
 290 295 300

Lys Lys Met Gln Met Val Ser Asn Ile Ser Phe Phe Ala Met Phe Val  
 305 310 315 320

Met Tyr Phe Leu Thr Ala Ile Phe Gly Tyr Leu Thr Phe Tyr Asp Asn  
 325 330 335

Val Gln Ser Asp Leu Leu His Lys Tyr Gln Ser Lys Asp Asp Ile Leu  
 340 345 350

Ile Leu Thr Val Arg Leu Ala Val Ile Val Ala Val Ile Leu Thr Val  
 355 360 365

Pro Val Leu Phe Phe Thr Val Arg Ser Ser Leu Phe Glu Leu Ala Lys  
 370 375 380

Lys Thr Lys Phe Asn Leu Cys Arg His Thr Val Val Thr Cys Ile Leu  
 385 390 395 400

Leu Val Val Ile Asn Leu Leu Val Ile Phe Ile Pro Ser Met Lys Asp  
 405 410 415

Ile Phe Gly Val Val Gly Val Thr Ser Ala Asn Met Leu Ile Phe Ile  
 420 425 430

Leu Pro Ser Ser Leu Tyr Leu Lys Ile Thr Asp Gln Asp Gly Asp Lys  
 435 440 445

Gly Thr Gln Arg Ile Trp Ala Ala Leu Phe Leu Gly Leu Gly Val Leu  
 450 455 460

Phe Ser Leu Val Ser Ile Pro Leu Val Ile Tyr Asp Trp Ala Cys Ser  
 465 470 475 480

Ser Ser Ser Asp Glu Gly His  
 485

<210> 251  
 <211> 528  
 <212> PRT  
 <213> Homo sapiens

<400> 251

Met Ala Gly Ser Asp Thr Ala Pro Phe Leu Ser Gln Ala Asp Asp Pro  
 1 5 10 15

Asp Asp Gly Pro Val Pro Gly Thr Pro Gly Leu Pro Gly Ser Thr Gly  
 20 25 30

Asn Pro Lys Ser Glu Glu Pro Glu Val Pro Asp Gln Glu Gly Leu Gln  
 35 40 45

Arg Ile Thr Gly Leu Ser Pro Gly Arg Ser Ala Leu Ile Val Ala Val  
 50 55 60

Leu Cys Tyr Ile Asn Leu Leu Asn Tyr Met Asp Arg Phe Thr Val Ala  
 65 70 75 80

Gly Val Leu Pro Asp Ile Glu Gln Phe Phe Asn Ile Gly Asp Ser Ser  
 85 90 95

Ser Gly Leu Ile Gln Thr Val Phe Ile Ser Ser Tyr Met Val Leu Ala  
 100 105 110

Pro Val Phe Gly Tyr Leu Gly Asp Arg Tyr Asn Arg Lys Tyr Leu Met

115                                      120                                      125  
 Cys Gly Gly Ile Ala Phe Trp Ser Leu Val Thr Leu Gly Ser Ser Phe  
     130                                      135                                      140  
 Ile Pro Gly Glu His Phe Trp Leu Leu Leu Leu Thr Arg Gly Leu Val  
     145                                      150                                      155                                      160  
 Gly Val Gly Glu Ala Ser Tyr Ser Thr Ile Ala Pro Thr Leu Ile Ala  
                                     165                                      170                                      175  
 Asp Leu Phe Val Ala Asp Gln Arg Ser Arg Met Leu Ser Ile Phe Tyr  
                                     180                                      185                                      190  
 Phe Ala Ile Pro Val Gly Ser Gly Leu Gly Tyr Ile Ala Gly Ser Lys  
                                     195                                      200                                      205  
 Val Lys Asp Met Ala Gly Asp Trp His Trp Ala Leu Arg Val Thr Pro  
                                     210                                      215                                      220  
 Gly Leu Gly Val Val Ala Val Leu Leu Leu Phe Leu Val Val Arg Glu  
     225                                      230                                      235                                      240  
 Pro Pro Arg Gly Ala Val Glu Arg His Ser Asp Leu Pro Pro Leu Asn  
                                     245                                      250                                      255  
 Pro Thr Ser Trp Trp Ala Asp Leu Arg Ala Leu Ala Arg Asn Pro Ser  
                                     260                                      265                                      270  
 Phe Val Leu Ser Ser Leu Gly Phe Thr Ala Val Ala Phe Val Thr Gly  
                                     275                                      280                                      285  
 Ser Leu Ala Leu Trp Ala Pro Ala Phe Leu Leu Arg Ser Arg Val Val  
                                     290                                      295                                      300  
 Leu Gly Glu Thr Pro Pro Cys Leu Pro Gly Asp Ser Cys Ser Ser Ser  
     305                                      310                                      315                                      320  
 Asp Ser Leu Ile Phe Gly Leu Ile Thr Cys Leu Thr Gly Val Leu Gly  
                                     325                                      330                                      335  
 Val Gly Leu Gly Val Glu Ile Ser Arg Arg Leu Arg His Ser Asn Pro  
                                     340                                      345                                      350



Arg Ala Asp Pro Leu Val Cys Ala Thr Gly Leu Leu Gly Ser Ala Pro  
 355 360 365

Phe Leu Phe Leu Ser Leu Ala Cys Ala Arg Gly Ser Ile Val Ala Thr  
 370 375 380

Tyr Ile Phe Ile Phe Ile Gly Glu Thr Leu Leu Ser Met Asn Trp Ala  
 385 390 395 400

Ile Val Ala Asp Ile Leu Leu Tyr Val Val Ile Pro Thr Arg Arg Ser  
 405 410 415

Thr Ala Glu Ala Phe Gln Ile Val Leu Ser His Leu Leu Gly Asp Ala  
 420 425 430

Gly Ser Pro Tyr Leu Ile Gly Leu Ile Ser Asp Arg Leu Arg Arg Asn  
 435 440 445

Trp Pro Pro Ser Phe Leu Ser Glu Phe Arg Ala Leu Gln Phe Ser Leu  
 450 455 460

Met Leu Cys Ala Phe Val Gly Ala Leu Gly Gly Ala Ala Phe Leu Gly  
 465 470 475 480

Thr Ala Ile Phe Ile Glu Ala Asp Arg Arg Arg Ala Gln Leu His Val  
 485 490 495

Gln Gly Leu Leu His Glu Ala Gly Ser Thr Asp Asp Arg Ile Val Val  
 500 505 510

Pro Gln Arg Gly Arg Ser Thr Arg Val Pro Val Ala Ser Val Leu Ile  
 515 520 525

<210> 252  
 <211> 418  
 <212> PRT  
 <213> Homo sapiens

<400> 252

Met Ala Pro Thr Gln Gly Pro Arg Ala Pro Leu Glu Phe Gly Gly Pro  
 1 5 10 15

Leu Gly Ala Ala Ala Leu Leu Leu Leu Leu Pro Ala Thr Met Phe His  
 20 25 30

Leu Leu Leu Ala Ala Arg Ser Gly Pro Ala Arg Leu Leu Gly Pro Pro  
 35 40 45

Ala Ser Leu Pro Gly Leu Glu Val Leu Trp Ser Pro Arg Ala Leu Leu  
 50 55 60

Leu Trp Leu Ala Trp Leu Gly Leu Gln Ala Ala Leu Tyr Leu Leu Pro  
 65 70 75 80

Ala Arg Lys Val Ala Glu Gly Gln Glu Leu Lys Asp Lys Ser Arg Leu  
 85 90 95

Arg Tyr Pro Ile Asn Gly Phe Gln Ala Leu Val Leu Thr Ala Leu Leu  
 100 105 110

Val Gly Leu Gly Met Ser Ala Gly Leu Pro Leu Gly Ala Leu Pro Glu  
 115 120 125

Met Leu Leu Pro Leu Ala Phe Val Ala Thr Leu Thr Ala Phe Ile Phe  
 130 135 140

Ser Leu Phe Leu Tyr Met Lys Ala Gln Val Ala Pro Val Ser Ala Leu  
 145 150 155 160

Ala Pro Gly Gly Asn Ser Gly Asn Pro Ile Tyr Asp Phe Phe Leu Gly  
 165 170 175

Arg Glu Leu Asn Pro Arg Ile Cys Phe Phe Asp Phe Lys Tyr Phe Cys  
 180 185 190

Glu Leu Arg Pro Gly Leu Ile Gly Trp Val Leu Ile Asn Leu Ala Leu  
 195 200 205

Leu Met Lys Glu Ala Glu Leu Arg Gly Ser Pro Ser Leu Ala Met Trp  
 210 215 220

Leu Val Asn Gly Phe Gln Leu Leu Tyr Val Gly Asp Ala Leu Trp His  
 225 230 235 240

Glu Glu Ala Val Leu Thr Thr Met Asp Ile Thr His Asp Gly Phe Gly

Ile Tyr

<400> 253

449

Glu Gly Gln Ile Leu Glu Pro Ile Gly Thr Glu Ser Lys Val Ser Gly  
 20 25 30

Lys Asn Lys Glu Phe Ser Ala Asp Gln Met Ser Glu Asn Thr Asp Gln  
 35 40 45

Ser Asp Ala Ala Glu Leu Asn His Lys Glu Glu His Ser Leu His Val  
 50 55 60

Gln Asp Pro Ser Ser Ser Ser Lys Lys Asp Leu Lys Ser Ala Val Leu  
 65 70 75 80

Ser Glu Lys Ala Gly Phe Asn Tyr Glu Ser Pro Ser Lys Gly Gly Asn  
 85 90 95

Phe Pro Ser Phe Pro His Asp Glu Val Thr Asp Arg Asn Met Leu Ala  
 100 105 110

Phe Ser Ser Pro Ala Ala Gly Gly Val Cys Glu Pro Leu Lys Ser Pro  
 115 120 125

Gln Arg Ala Glu Ala Asp Asp Pro Gln Asp Met Ala Cys Thr Pro Ser  
 130 135 140

Gly Asp Ser Leu Glu Thr Lys Glu Asp Gln Lys Met Ser Pro Lys Ala  
 145 150 155 160

Thr Glu Glu Thr Gly Gln Ala Gln Ser Gly Gln Ala Asn Cys Gln Gly  
 165 170 175

Leu Ser Pro Val Ser Val Ala Ser Lys Asn Pro Gln Val Pro Ser Asp  
 180 185 190

Gly Gly Val Arg Leu Asn Lys Ser Lys Thr Asp Leu Leu Val Asn Asp  
 195 200 205

Asn Pro Asp Pro Ala Pro Leu Ser Pro Glu Leu Gln Asp Phe Lys Cys  
 210 215 220

Asn Ile Cys Gly Tyr Gly Tyr Tyr Gly Asn Asp Pro Thr Asp Leu Ile  
 225 230 235 240

Lys His Phe Arg Lys Tyr His Leu Gly Leu His Asn Arg Thr Arg Gln  
 245 250 255  
 Asp Ala Glu Leu Asp Ser Lys Ile Leu Ala Leu His Asn Met Val Gln  
 260 265 270  
 Phe Ser His Ser Lys Asp Phe Gln Lys Val Asn Arg Ser Val Phe Ser  
 275 280 285  
 Gly Val Leu Gln Asp Ile Asn Ser Ser Arg Pro Val Leu Leu Asn Gly  
 290 295 300  
 Thr Tyr Asp Val Gln Val Thr Ser Gly Gly Thr Phe Ile Gly Ile Gly  
 305 310 315 320  
 Arg Lys Thr Pro Asp Cys Gln Gly Asn Thr Lys Tyr Phe Arg Cys Lys  
 325 330 335  
 Phe Cys Asn Phe Thr Tyr Met Gly Asn Ser Ser Thr Glu Leu Glu Gln  
 340 345 350  
 His Phe Leu Gln Thr His Pro Asn Lys Ile Lys Ala Ser Leu Pro Ser  
 355 360 365  
 Ser Glu Val Ala Lys Pro Ser Glu Lys Asn Ser Asn Lys Ser Ile Pro  
 370 375 380  
 Ala Leu Gln Ser Ser Asp Ser Gly Asp Leu Gly Lys Trp Gln Asp Lys  
 385 390 395 400  
 Ile Thr Val Lys Ala Gly Asp Asp Thr Pro Val Gly Tyr Ser Val Pro  
 405 410 415  
 Ile Lys Pro Leu Asp Ser Ser Arg Gln Asn Gly Thr Glu Ala Thr Ser  
 420 425 430  
 Tyr Tyr Trp Cys Lys Phe Cys Ser Phe Ser Cys Glu Ser Ser Ser Ser  
 435 440 445  
 Leu Lys Leu Leu Glu His Tyr Gly Lys Gln His Gly Ala Val Gln Ser  
 450 455 460  
 Gly Gly Leu Asn Pro Glu Leu Asn Asp Lys Leu Ser Arg Gly Ser Val

452

Gln Ser Leu Leu Glu His Phe Asn Thr Val His Cys Gln Glu Gln Asp  
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 Ile Thr Thr Ala Asn Gly Glu Glu Asp Gly His Ala Ile Ser Thr Ile  
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 Lys Glu Glu Pro Lys Ile Asp Phe Arg Val Tyr Asn Leu Leu Thr Pro  
 740 745 750  
 Asp Ser Lys Met Gly Glu Pro Val Ser Glu Ser Val Val Lys Arg Glu  
 755 760 765  
 Lys Leu Glu Glu Lys Asp Gly Leu Lys Glu Lys Val Trp Thr Glu Ser  
 770 775 780  
 Ser Ser Asp Asp Leu Arg Asn Val Thr Trp Arg Gly Ala Asp Ile Leu  
 785 790 795 800  
 Arg Gly Ser Pro Ser Tyr Thr Gln Ala Ser Leu Gly Leu Leu Thr Pro  
 805 810 815  
 Val Ser Gly Thr Gln Glu Gln Thr Lys Thr Leu Arg Asp Ser Pro Asn  
 820 825 830  
 Val Glu Ala Ala His Leu Ala Arg Pro Ile Tyr Gly Leu Ala Val Glu  
 835 840 845  
 Thr Lys Gly Phe Leu Gln Gly Ala Pro Ala Gly Gly Glu Lys Ser Gly  
 850 855 860  
 Ala Leu Pro Gln Gln Tyr Pro Ala Ser Gly Glu Asn Lys Ser Lys Asp  
 865 870 875 880  
 Glu Ser Gln Ser Leu Leu Arg Arg Arg Arg Gly Ser Gly Val Phe Cys  
 885 890 895  
 Ala Asn Cys Leu Thr Thr Lys Thr Ser Leu Trp Arg Lys Asn Ala Asn  
 900 905 910  
 Gly Gly Tyr Val Cys Asn Ala Cys Gly Leu Tyr Gln Lys Leu His Ser  
 915 920 925

Thr Pro Arg Pro Leu Asn Ile Ile Lys Gln Asn Asn Gly Glu Gln Ile  
 930 935 940

Ile Arg Arg Arg Thr Arg Lys Arg Leu Asn Pro Glu Ala Leu Gln Ala  
 945 950 955 960

Glu Gln Leu Asn Lys Gln Gln Arg Gly Ser Asn Glu Glu Gln Val Asn  
 965 970 975

Gly Ser Pro Leu Glu Arg Arg Ser Glu Asp His Leu Thr Glu Ser His  
 980 985 990

Gln Arg Glu Ile Pro Leu Pro Ser Leu Ser Lys Tyr Glu Ala Gln Gly  
 995 1000 1005

Ser Leu Thr Lys Ser His Ser Ala Gln Gln Pro Val Leu Val Ser  
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Gln Thr Leu Asp Ile His Lys Arg Met Gln Pro Leu His Ile Gln  
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Ile Lys Ser Pro Gln Glu Ser Thr Gly Asp Pro Gly Asn Ser Ser  
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Ser Val Ser Glu Gly Lys Gly Ser Ser Glu Arg Gly Ser Pro Ile  
 1055 1060 1065

Glu Lys Tyr Met Arg Pro Ala Lys His Pro Asn Tyr Ser Pro Pro  
 1070 1075 1080

Gly Ser Pro Ile Glu Lys Tyr Gln Tyr Pro Leu Phe Gly Leu Pro  
 1085 1090 1095

Phe Val His Asn Asp Phe Gln Ser Glu Ala Asp Trp Leu Arg Phe  
 1100 1105 1110

Trp Ser Lys Tyr Lys Leu Ser Val Pro Gly Asn Pro His Tyr Leu  
 1115 1120 1125

Ser His Val Pro Gly Leu Pro Asn Pro Cys Gln Asn Tyr Val Pro  
 1130 1135 1140



Tyr Pro Thr Phe Asn Leu Pro Pro His Phe Ser Ala Val Gly Ser  
 1145 1150 1155

Asp Asn Asp Ile Pro Leu Asp Leu Ala Ile Lys His Ser Arg Pro  
 1160 1165 1170

Gly Pro Thr Ala Asn Gly Ala Ser Lys Glu Lys Thr Lys Ala Pro  
 1175 1180 1185

Pro Asn Val Lys Asn Glu Gly Pro Leu Asn Val Val Lys Thr Glu  
 1190 1195 1200

Lys Val Asp Arg Ser Thr Gln Asp Glu Leu Ser Thr Lys Cys Val  
 1205 1210 1215

His Cys Gly Ile Val Phe Leu Asp Glu Val Met Tyr Ala Leu His  
 1220 1225 1230

Met Ser Cys His Gly Asp Ser Gly Pro Phe Gln Cys Ser Ile Cys  
 1235 1240 1245

Gln His Leu Cys Thr Asp Lys Tyr Asp Phe Thr Thr His Ile Gln  
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Pro Lys Glu  
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 35 40 45

Val Tyr Val Ala Ala Pro Gly Glu Ser Leu Glu Val Arg Cys Leu Leu  
 50 55 60

Lys Asp Ala Ala Val Ile Ser Trp Thr Lys Asp Gly Val His Leu Gly  
 65 70 75 80

Pro Asn Asn Arg Thr Val Leu Ile Gly Glu Tyr Leu Gln Ile Lys Gly  
 85 90 95

Ala Thr Pro Arg Asp Ser Gly Leu Tyr Ala Cys Thr Ala Ser Arg Thr  
 100 105 110

Val Asp Ser Glu Thr Trp Tyr Phe Met Val Asn Val Thr Asp Ala Ile  
 115 120 125

Ser Ser Gly Asp Asp Glu Asp Asp Thr Asp Gly Ala Glu Asp Phe Val  
 130 135 140

Ser Glu Asn Ser Asn Asn Lys Arg Ala Pro Tyr Trp Thr Asn Thr Glu  
 145 150 155 160

Lys Met Glu Lys Arg Leu His Ala Val Pro Ala Ala Asn Thr Val Lys  
 165 170 175

Phe Arg Cys Pro Ala Gly Gly Asn Pro Met Pro Thr Met Arg Trp Leu  
 180 185 190

Lys Asn Gly Lys Glu Phe Lys Gln Glu His Arg Ile Gly Gly Tyr Lys  
 195 200 205

Val Arg Asn Gln His Trp Ser Leu Ile Met Glu Ser Val Val Pro Ser  
 210 215 220

Asp Lys Gly Asn Tyr Thr Cys Val Val Glu Asn Glu Tyr Gly Ser Ile  
 225 230 235 240

Asn His Thr Tyr His Leu Asp Val Val Glu Arg Ser Pro His Arg Pro  
 245 250 255

Ile Leu Gln Ala Gly Leu Pro Ala Asn Ala Ser Thr Val Val Gly Gly  
 260 265 270

Asp Val Glu Phe Val Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile  
 275 280 285

Gln Trp Ile Lys His Val Glu Lys Asn Gly Ser Lys Tyr Gly Pro Asp  
 290 295 300

Gly Leu Pro Tyr Leu Lys Val Leu Lys His Ser Gly Ile Asn Ser Ser  
 305 310 315 320

Asn Ala Glu Val Leu Ala Leu Phe Asn Val Thr Glu Ala Asp Ala Gly  
 325 330 335

Glu Tyr Ile Cys Lys Val Ser Asn Tyr Ile Gly Gln Ala Asn Gln Ser  
 340 345 350

Ala Trp Leu Thr Val Leu Pro Lys Gln Gln Ala Pro Gly Arg Glu Lys  
 355 360 365

Glu Ile Thr Ala Ser Pro Asp Tyr Leu Glu Ile Ala Ile Tyr Cys Ile  
 370 375 380

Gly Val Phe Leu Ile Ala Cys Met Val Val Thr Val Ile Leu Cys Arg  
 385 390 395 400

Met Lys Asn Thr Thr Lys Lys Pro Asp Phe Ser Ser Gln Pro Ala Val  
 405 410 415

His Lys Leu Thr Lys Arg Ile Pro Leu Arg Arg Gln Val Thr Val Ser  
 420 425 430

Ala Glu Ser Ser Ser Met Asn Ser Asn Thr Pro Leu Val Arg Ile  
 435 440 445

Thr Thr Arg Leu Ser Ser Thr Ala Asp Thr Pro Met Leu Ala Gly Val  
 450 455 460

Ser Glu Tyr Glu Leu Pro Glu Asp Pro Lys Trp Glu Phe Pro Arg Asp  
 465 470 475 480

Lys Leu Thr Leu Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln Val  
 485 490 495

Val Met Ala Glu Ala Val Gly Ile Asp Lys Asp Lys Pro Lys Glu Ala  
500 505 510

Val Thr Val Ala Val Lys Met Leu Lys Asp Asp Ala Thr Glu Lys Asp  
515 520 525

Leu Ser Asp Leu Val Ser Glu Met Glu Met Met Lys Met Ile Gly Lys  
530 535 540

His Lys Asn Ile Ile Asn Leu Leu Gly Ala Cys Thr Gln Asp Gly Pro  
545 550 555 560

Leu Tyr Val Ile Val Glu Tyr Ala Ser Lys Gly Asn Leu Arg Glu Tyr  
565 570 575

Leu Arg Ala Arg Arg Pro Pro Gly Met Glu Tyr Ser Tyr Asp Ile Asn  
580 585 590

Arg Val Pro Glu Glu Gln Met Thr Phe Lys Asp Leu Val Ser Cys Thr  
595 600 605

Tyr Gln Leu Ala Arg Gly Met Glu Tyr Leu Ala Ser Gln Lys Cys Ile  
610 615 620

His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Thr Glu Asn Asn Val  
625 630 635 640

Met Lys Ile Ala Asp Phe Gly Leu Ala Arg Asp Ile Asn Asn Ile Asp  
645 650 655

Tyr Tyr Lys Lys Thr Thr Asn Gly Arg Leu Pro Val Lys Trp Met Ala  
660 665 670

Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr His Gln Ser Asp Val Trp  
675 680 685

Ser Phe Gly Val Leu Met Trp Glu Ile Phe Thr Leu Gly Gly Ser Pro  
690 695 700

Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe Lys Leu Leu Lys Glu Gly  
705 710 715 720

His Arg Met Asp Lys Pro Ala Asn Cys Thr Asn Glu Leu Tyr Met Met

725

730

735

Met Arg Asp Cys Trp His Ala Val Pro Ser Gln Arg Pro Thr Phe Lys  
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Gln Leu Val Glu Asp Leu Asp Arg Ile Leu Thr Leu Thr Thr Asn Glu  
 755 760 765

Glu Tyr Leu Asp Leu Ser Gln Pro Leu Glu Gln Tyr Ser Pro Ser Tyr  
 770 775 780

Pro Asp Thr Arg Ser Ser Cys Ser Ser Gly Asp Asp Ser Val Phe Ser  
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Pro Asp Pro Met Pro Tyr Glu Pro Cys Leu Pro Gln Tyr Pro His Ile  
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Asn Gly Ser Val Lys Thr  
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Glu Phe Phe Ala Asp Val Trp Arg Ile Cys Thr Asn Asn Thr Asn Cys  
 35 40 45

Thr Val Ile Asn Asp Ser Phe Gln Glu Tyr Ser Thr Leu Gln Ala Val  
 50 55 60

Gln Ala Thr Met Ile Leu Ser Thr Ile Leu Cys Cys Ile Ala Phe Phe  
 65 70 75 80

Ile Phe Val Leu Gln Leu Phe Arg Leu Lys Gln Gly Glu Arg Phe Val  
 85 90 95

Leu Thr Ser Ile Ile Gln Leu Met Ser Cys Leu Cys Val Met Ile Ala  
 100 105 110

Ala Ser Ile Tyr Thr Asp Arg Arg Glu Asp Ile His Asp Lys Asn Ala  
 115 120 125

Lys Phe Tyr Pro Val Thr Arg Glu Gly Ser Tyr Gly Tyr Ser Tyr Ile  
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Leu Ala Trp Val Ala Phe Ala Cys Thr Phe Ile Ser Gly Met Met Tyr  
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Leu Ile Leu Arg Lys Arg Lys  
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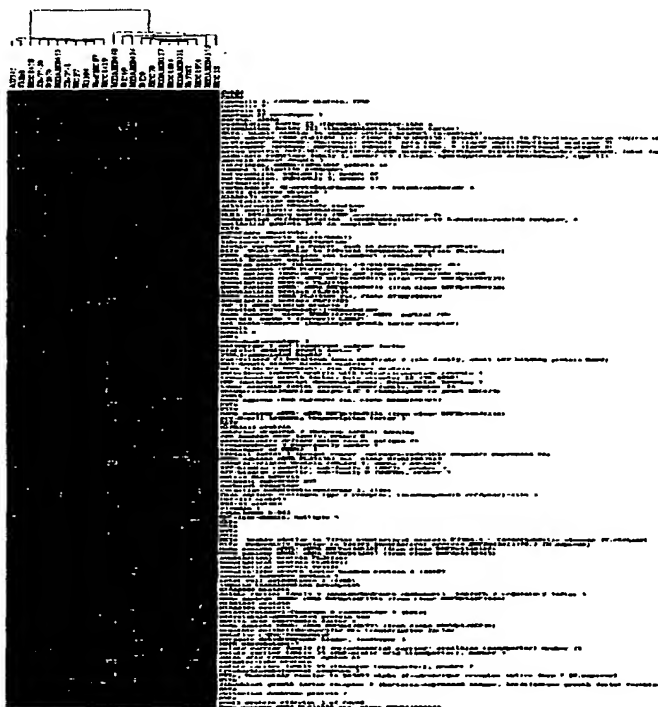
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(54) Title: IDENTIFICATION OF POLYNUCLEOTIDES FOR PREDICTING ACTIVITY OF COMPOUNDS THAT INTER-  
ACT WITH AND/OR MODULATE PROTEIN TYROSINE KINASES AND/OR PROTEIN TYROSINE KINASE PATHWAYS IN  
BREAST CELLS



(57) Abstract: The present invention describes polynucleotides that have been discovered to correlate to the relative intrinsic sensitivity or resistance of cells, e.g., breast cell lines, to treatment with compounds that interact with and modulate, e.g., inhibit, protein tyrosine kinases, such as, for example, members of the Src family of tyrosine kinases, e.g., Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as other protein tyrosine kinases, including, Bcr-abl, Jak, PDGFR, c-kit and Eph receptors. These polynucleotides have been shown, through a weighted voting cross validation program, to have utility in predicting the resistance and sensitivity of breast cell lines to the compounds. The expression level or phosphorylation status of some polynucleotides is regulated by treatment with a particular protein tyrosine kinase inhibitor compound, thus indicating that these polynucleotides are involved in the protein tyrosine kinase signal transduction pathway, e.g., Src tyrosine kinase. Such polynucleotides, whose expression levels correlate highly with drug sensitivity or resistance and which are modulated by treatment with the compounds, comprise polynucleotide predictor or marker sets useful in methods of predicting drug response, and as prognostic or diagnostic indicators in disease management, particularly in those disease areas, e.g., breast cancer, in which signaling through the protein tyrosine kinase pathway, such as the Src tyrosine kinase pathway, is involved with

the disease process.

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